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(54) Title: TUMOR ANTIGEN DERIVED GENE-16 (TADG-16): A NOVEL EXTRACELLULAR SERINE PROTEASE AND USES THEREOF

(57) Abstract: The present invention provides a DNA encoding a TADG-16 protein selected from the group consisting of: (a) isolated DNA which encodes a TADG-16 protein; (b) isolated DNA which hybridizes to isolated DNA of (a) above and which encodes a TADG-16 protein; and (c) isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein. Also provided is a vector capable of expressing the DNA of the present invention adapted for expression in a recombinant cell and regulatory elements necessary for expression of the DNA in the cell.

TUMOR ANTIGEN DERIVED GENE-16 (TADG-16): A NOVEL EXTRACELLULAR SERINE PROTEASE AND USES THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates generally to the fields of cellular biology and the diagnosis of neoplastic disease. More specifically, the present invention relates to an extracellular serine protease termed Tumor Antigen Derived Gene-16 (TADG-16), which is expressed in normal ovaries and testes, as well as certain ovarian carcinomas.

Description of the Related Art

To date, ovarian cancer remains the number one killer of women with gynecologic malignant hyperplasia. Approximately 75% of women diagnosed with such cancers are already at the high-stage (III and IV) of the disease at their initial diagnosis. During the past 20 years, neither diagnosis nor five year survival have greatly improved for these patients. This is substantially due to the significant number of high-stage initial detections of the disease. Therefore, the challenge remains to develop new markers to improve early diagnosis, and thereby reduce the percentage of high-stage initial diagnoses.

A good tumor marker useful as an indicator of early disease is needed. Extra-cellular proteases have already been implicated in the growth, spread and metastatic progression of many cancers, thereby implying that some extracellular proteases may be candidates for marker of neoplastic development. This is in part due to the ability of malignant cells not only to grow *in situ*, but to dissociate from the primary tumor and to invade new surfaces (metastasize). The ability to disengage from one tissue and re-engage the surface of another tissue is what results in the morbidity and mortality associated with this disease.

In order for malignant cells to grow, spread or metastasize, they must have the capacity to invade local host tissue, dissociate or shed from the primary tumor, and for metastasis to

occur, enter and survive in the bloodstream, implant by invasion into the surface of the target organ and establish an environment conducive for new colony growth (including the induction of angiogenic and growth factors). During this progression, natural tissue barriers have to be degraded, including basement membranes and connective tissue. These barriers further include collagen, laminin, proteoglycans and extracellular matrix glycoproteins, such as fibronectin.

Degradation of these natural barriers, both surrounding the primary tumor and at sites of metastatic invasion, is believed to be brought about by the action of extracellular proteases. Proteases have been classified into four families: serine proteases, metallo-proteases, aspartic proteases and cysteine proteases. Many proteases have been shown to be involved in the human disease process and these enzymes are targets for inhibition by new therapeutic agents.

Certain individual proteases have already been shown to be induced and overexpressed in a diverse group of cancers, and as such, are potential candidates for markers useful for early diagnosis and possibly therapeutic intervention. Examples of proteases, encompassing members of the metallo-proteases, serine proteases, and cysteine proteases, are listed below.

TABLE 1

Protease Expression in Various Cancers

	Gastric	Brain	Breast	Ovarian
Serine Proteases	uPA PAI-1	uPA PAI-1 uPA tPA	NES-1 uPA	NES-1 PAI-2
Cysteine Proteases	Cathepsin B Cathepsin L	Cathepsin L	Cathepsin B Cathepsin L	Cathepsin B Cathepsin L
Metallo-proteases	Matrilysin* Collagenase* Stromelysin-1*	Matrilysin Stromelysin Gelatinase B	Stromelysin-3 MMP-8 MMP-9 Gelatinase A	MMP-2

uPA, Urokinase-type plasminogen activator; tPA, Tissue-type plasminogen activator; PAI-I, Plasminogen activator 0 inhibitors; PAI-2, Plasminogen activator inhibitors; NES-1, Normal epithelial cell-specific-1; MMP, Matrix P metallo-protease. *Overexpressed in gastrointestinal ulcers.

Significantly, there is a good body of evidence supporting the down regulation or inhibition of individual proteases and a subsequent reduction in invasive capacity or malignancy. In work by Clark *et al.*, (*Peptides*, 14, 1021-8 (1993)) inhibition of *in vitro* growth of human small cell lung cancer was demonstrated using a general serine protease inhibitor. More recently, Torres-Rosedo *et al.*, (*Proc. Natl. Acad. Sci. USA,* 90, 7181-7185 (1993)) demonstrated an

inhibition of hepatoma tumor cell growth using specific antisense inhibitors for the serine protease hepsin gene. Metastatic potential has also been shown to be reduced using a synthetic inhibitor (batimastat) of metallo-protease in a mouse model with melanoma cells. Powell *et al.* (*Cancer Research*, 53, 417-422 (1993)) presented evidence to confirm that the expression of extracellular proteases in relatively non-invasive tumor cells enhances their malignant progression using a tumor-genic, but non-metastatic, prostate cell line. Specifically, Powell *et al.* demonstrated enhanced metastasis after introducing and expressing the PUMP-1 metallo-protease gene. There is also a body of data to support the notion that expression of cell surface proteases on relatively non-metastatic cell types increases the invasive potential of such cells.

Extracellular proteases have been directly associated with tumor growth, shedding of tumor cells and invasion of target organs by tumors. Individual classes of proteases are involved in, but not limited to, (a) digestion of stroma surrounding the initial tumor area; (b) digestion of the cellular adhesion molecules to allow dissociation of tumor cells; and (c) invasion of the basement membrane for metastatic growth and the activation of both tumor growth factors and angiogenic factors.

Interfering in the intracellular signal transduction pathways provides mechanisms for numerous therapeutic

applications. While several proteins have been identified that interfere with various signal transduction mechanisms, novel proteins involved in signal transduction pathways are important to provide alternatives for therapy and drug development.

The prior art is deficient in that the prior art lacks the nucleotide and amino acid sequences corresponding to tumor antigen-derived gene 16 (TADG-16). The prior art further lacks effective means of screening to identify proteases, specifically TADG-16, expressed in normal ovaries and testes and certain ovarian carcinomas. The present invention fulfills this longstanding need and desire in the art.

SUMMARY OF THE INVENTION

This invention describes a new serine protease enzyme. The TADG-16 enzyme contains the characteristic features of a serine protease, including the conserved catalytic triad (His-Asp-Ser) and a secretion signal sequence. The TADG-16 transcript is present in carcinomas and normal ovarian tissues as well as in normal testes. Because TADG-16 is secreted and has a potential for extracellular activation, TADG-16 may have a role in normal or aberrant physiological activity of ovary or testes.

In one embodiment of the present invention, there is provided a DNA encoding a tumor antigen-derived gene (TADG-16) protein, selected from the following: (a) an isolated DNA which encodes a TADG-16 protein; (b) an isolated DNA which hybridizes under high stringency conditions to the isolated DNA of (a) above and which encodes a TADG-16 protein; and (c) an isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein. The embodiment further includes a vector comprising the TADG-16 DNA and regulatory elements necessary for expression of the DNA in a cell. Additionally embodied is a vector in which the TADG-16 DNA is positioned in reverse orientation relative to the regulatory elements such that TADG-16 antisense mRNA is produced.

In another embodiment of the present invention, there is provided an isolated and purified TADG-16 protein coded for by DNA selected from the following: (a) an isolated DNA which encodes a TADG-16 protein; (b) an isolated DNA which hybridizes under high stringency conditions to isolated DNA of (a) above and which encodes a TADG-16 protein; and (c) an isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein.

In yet another embodiment of the present invention, there is provided a method for detecting TADG-16 mRNA in a sample, comprising the steps of (a) contacting a sample with a probe which is specific for TADG-16; and (b) detecting binding of the probe to TADG-16 mRNA in the sample. In still yet another embodiment of the present invention, there is provided a kit for detecting TADG-16 mRNA, comprising an oligonucleotide probe specific for TADG-16. A label for detection is further embodied in the kit.

The present invention additionally embodies a method of detecting TADG-16 protein in a sample, comprising the steps of (a) contacting a sample with an antibody which is specific for TADG-16 or a fragment thereof; and (b) detecting binding of the antibody to TADG-16 protein in the sample. Similarly, the present invention also embodies a kit for detecting TADG-16 protein, comprising an antibody specific for TADG-16 protein or a fragment thereof. Means for detection of the antibody is further embodied in the kit.

In another embodiment, the present invention provides an antibody specific for the TADG-16 protein or a fragment thereof.

In yet another embodiment, the present invention provides a method of screening for compounds that inhibit TADG-16, comprising the steps of (a) contacting a sample comprising TADG-16 protein with a compound; and (b) assaying for TADG-16 protease activity. Typically, a decrease in the TADG-16 protease activity in the

presence of the compound relative to TADG-16 protease activity in the absence of the compound is indicative of a compound that inhibits TADG-16.

In still yet another embodiment of the present invention, there is provided a method of inhibiting expression of TADG-16 in a cell, comprising the step of (a) introducing a vector into a cell, whereupon expression of the vector produces TADG-16 antisense mRNA in the cell which hybridizes to endogenous TADG-16 mRNA, thereby inhibiting expression of TADG-16 in the cell.

Further embodied by the present invention, there is provided a method of inhibiting a TADG-16 protein in a cell, comprising the step of (a) introducing an antibody specific for a TADG-16 protein or a fragment thereof into a cell, whereupon binding of the antibody to the TADG-16 protein inhibits the TADG-16 protein.

In another embodiment of the present invention, there is provided a method of targeted therapy to an individual, comprising the step of (a) administering a compound containing a targeting moiety and a therapeutic moiety to an individual, wherein the targeting moiety is specific for TADG-16.

In another embodiment of the present invention, there is provided a method of diagnosing cancer in an individual, comprising the steps of (a) obtaining a biological sample from an individual; and (b) detecting TADG-16 in the sample. Typically, the presence of

TADG-16 in the sample is indicative of the presence of carcinoma in the individual and the absence of TADG-16 in the sample is indicative of the absence of carcinoma in the individual.

In another embodiment of the present invention, there is provided a method of vaccinating an individual against TADG-16, comprising the steps of (a) inoculating an individual with a TADG-16 protein or fragment thereof that lacks TADG-16 protease activity. It is intended that inoculation with the TADG-16 protein or fragment thereof elicits an immune response in the individual, thereby vaccinating the individual against TADG-16.

In another embodiment of the present invention, there is provided an immunogenic composition, comprising an immunogenic fragment of TADG-16 and an appropriate adjuvant.

Other and further aspects, features, and advantages of the present invention will be apparent from the following description of the presently preferred embodiments of the invention given for the purpose of disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

So that the matter in which the above-recited features, advantages and objects of the invention, as well as others which will

become clear, are attained and can be understood in detail, more particular descriptions of the invention briefly summarized above may be had by reference to certain embodiments thereof which are illustrated in the appended drawings. These drawings form a part of the specification. It is to be noted, however, that the appended drawings illustrate preferred embodiments of the invention and therefore are not to be considered limiting in their scope.

Figure 1 shows an alignment of a portion of the TADG-16 protein sequence (SEQ ID No. 7) with other known proteases (Prom, Protease M (SEQ ID No. 3); Try1, Trypsinogen 1 (SEQ ID No. 4); SCCE, Stratum corneum chymotryptic like enzyme (SEQ ID No. 5); and Heps, Hepsin (SEQ ID No. 6)).

Figure 2 shows Northern blot analysis of multiple human tissues using the radioactively labeled catalytic domain as a probe. The 1.4 Kb TADG-16 transcript is present in normal human testes and in certain ovarian tumors, but is not detectable at significant levels in other tissues examined. Hybridization of mRNA to β-tubulin is shown as an internal control.

Figure 3A shows the nucleotide and predicted amino acid sequence of the original subclone from the WISH cDNA containing the TADG-16 catalytic domain. **Figure 3B** shows a sequence identified from the EST database (Accession #AA620757) with homology to the TADG-16 catalytic domain (encoding bases 614 to 1129) and

including the 3' untranslated region and poly(A) tail of the TADG-16 transcript.

Figure 4 shows the nucleotide sequence of the TADG-16 cDNA and the predicted amino acid sequence. The cDNA corresponding to TADG-16 contains a Kozak's consensus sequence (boxed nucleotides) for the initiation of translation from which a putative protein of 314 amino acids is encoded. The protein contains a secretion signal sequence (italicized) and the conserved amino acids of the catalytic triad of the serine protease family (circled) in the appropriate context (underlined residues). The cDNA also contains a polyadenylation sequence in the 3' untranslated region (underlined nucleotides).

Figure 5 shows TADG-16 (and β-tubulin) expression in normal and carcinoma cell lines.

Figure 6 shows TADG-16 expression in normal (N), benign (B), low malignant potential (LMP) tumors and carcinomas (C). **Figure 6A** shows quantitative PCR of TADG-16 (250 bp) and internal control, β-tubulin (470 bp). *Lanes 1-3*, normal ovary (cases 5-7, respectively); *Lanes 4-5*, benign mucinous adenoma tumor (cases 8 & 11, respectively); *Lane 6*, serous LMP tumor (case 14); *Lanes 7-8*, clear cell carcinoma (cases 20 & 21, respectively); *Lanes 9-11*, serous adenocarcinoma (cases 22, 29 and 32, respectively); *Lane 12*, endometrioid adenocarcinoma (case 35). **Figure 6B** shows a graph

of expression of TADG-16 in normal ovaries and ovarian benign, LMP and carcinoma tumors.

DETAILED DESCRIPTION OF THE INVENTION

This invention describes a new serine protease enzyme complementary to the series of proteases already identified and characterized in ovarian carcinoma. The TADG-16 enzyme contains the characteristic features of all serine proteases, including the conserved catalytic triad of His-Asp-Ser and a signal secretion sequence. The transcript for this enzyme is present in carcinomas and normal ovarian tissues as well as in normal testes. Because TADG-16 is secreted and has a potential for extracellular activation, TADG-16 may have a role in normal or aberrant physiological activity (*i.e.*, normal or carcinomatous growth) of ovary or testes. Furthermore, because of the presence of TADG-16 mRNA in normal testes, there is a potential role for TADG-16 in normal testicular function (*e.g.*, sterility).

The TADG-16 cDNA is 1129 base pairs long (SEQ ID No. 1) and encodes a 314 amino acid protein (SEQ ID No. 2).

In accordance with the present invention there may be employed conventional molecular biology, microbiology, and

recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See, *e.g.*, Maniatis, Fritsch & Sambrook, "Molecular Cloning: A Laboratory Manual (1982); "DNA Cloning: A Practical Approach," Volumes I and II (D.N. Glover ed. 1985); "Oligonucleotide Synthesis" (M.J. Gait ed. 1984); "Nucleic Acid Hybridization" [B.D. Hames & S.J. Higgins eds. (1985)]; "Transcription and Translation" [B.D. Hames & S.J. Higgins eds. (1984)]; "Animal Cell Culture" [R.I. Freshney, ed. (1986)]; "Immobilized Cells And Enzymes" [IRL Press, (1986)]; B. Perbal, "A Practical Guide To Molecular Cloning" (1984).

Therefore, if appearing herein, the following terms shall have the definitions set out below.

As used herein, the term “cDNA” shall refer to the DNA copy of the mRNA transcript of a gene.

As used herein, the term “derived amino acid sequence” shall mean the amino acid sequence determined by reading the triplet sequence of nucleotide bases in the cDNA.

As used herein the term “screening a library” shall refer to the process of using a labeled probe to check whether, under the appropriate conditions, there is a sequence complementary to the probe present in a particular DNA library. In addition, “screening a library” could be performed by PCR.

As used herein, the term “PCR” refers to the Polymerase Chain Reaction that is the subject of U.S. Patent Nos. 4,683,195 and 4,683,202 to Mullis, as well as other improvements to the process/technique of PCR now known in the art.

The amino acid described herein are preferred to be in the "L" isomeric form. However, residues in the "D" isomeric form can be substituted for any L-amino acid residue, as long as the desired functional property of immunoglobulin-binding is retained by the polypeptide. NH_2 refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxy terminus of a polypeptide. In keeping with standard polypeptide nomenclature, *J Biol. Chem.*, 243:3552-59 (1969), abbreviations for amino acid residues are shown in Table 2.

TABLE 2

Symbol		Amino acid
1 Letter	3 Letter	
A	Ala	Alanine
C	Cys	Cysteine
D	Asp	Aspartic acid
E	Glu	Glutamic acid
F	Phe	Phenylalanine
G	Gly	Glycine
H	His	Histidine
I	Ile	Isoleucine
K	Lys	Lysine
L	Leu	Leucine
M	Met	Methionine
N	Asn	Asparagine

P	Pro	Proline
Q	Gln	Glutamine
R	Arg	Arginine
S	Ser	Serine
T	Thr	Threonine
V	Val	Valine
W	Trp	Tryptophan
Y	Tyr	Tyrosine

It should be noted that all amino-acid residue sequences are represented herein by formulae whose left and right orientation is in the conventional direction of amino-terminus to carboxy-terminus. Furthermore, it should be noted that a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further sequence of one or more amino-acid residues. The above table is presented to correlate the three-letter and one-letter notations which may appear alternately herein.

A "replicon" is any genetic element (*e.g.*, plasmid, chromosome, virus) that functions as an autonomous unit of DNA replication *in vivo*; *i.e.*, capable of replication under its own control.

A "vector" is a replicon, such as plasmid, phage or cosmid, to which another DNA segment may be attached so as to bring about the replication of the attached segment.

A "DNA molecule" refers to the polymeric form of deoxyribonucleotides (adenine, guanine, thymine, or cytosine) in its either single stranded form, or a double-stranded helix. This term refers only to the primary and secondary structure of the molecule,

and does not limit it to any particular tertiary forms. Thus, this term includes double-stranded DNA found, *inter alia*, in linear DNA molecules (*e.g.*, restriction fragments), viruses, plasmids, and chromosomes. The structure is discussed herein according to the normal convention of giving only the 5' to 3' sequence of the nontranscribed strand of DNA (*i.e.*, the strand having a sequence homologous to the mRNA).

An "origin of replication" refers to those DNA sequences that participate in DNA synthesis.

A DNA "coding sequence" is a double-stranded DNA sequence which is transcribed and translated into a polypeptide *in vivo* when placed under the control of appropriate regulatory sequences. The boundaries of the coding sequence are determined by a start codon at the 5' (amino) terminus and a translation stop codon at the 3' (carboxyl) terminus. A coding sequence can include, but is not limited to, prokaryotic sequences, cDNA from eukaryotic mRNA, genomic DNA sequences from eukaryotic (*e.g.*, mammalian) DNA, and even synthetic DNA sequences. A polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence.

Transcriptional and translational control sequences are DNA regulatory sequences, such as promoters, enhancers,

polyadenylation signals, terminators, and the like that provide for the expression of a coding sequence in a host cell.

A "promoter sequence" is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. For purposes of defining the present invention, the promoter sequence is bounded at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter sequence will be found a transcription initiation site, as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. Eukaryotic promoters often, but not always, contain "TATA" boxes and "CAT" boxes. Prokaryotic promoters contain Shine-Dalgarno sequences in addition to the -10 and -35 consensus sequences.

An "expression control sequence" is a DNA sequence that controls and regulates the transcription and translation of another DNA sequence. A coding sequence is "under the control" of transcriptional and translational control sequences in a cell when RNA polymerase transcribes the coding sequence into mRNA, which is then translated into the protein encoded by the coding sequence.

A "signal sequence" can be included near the coding sequence. This sequence encodes a signal peptide, N-terminal to the polypeptide, that communicates to the host cell to direct the polypeptide to the cell surface or secrete the polypeptide into the media, and this signal peptide is clipped off by the host cell before the protein leaves the cell. Signal sequences can be found associated with a variety of proteins native to prokaryotes and eukaryotes.

The term "oligonucleotide", as used herein in referring to the probe of the present invention, is defined as a molecule comprised of two or more ribonucleotides, preferably more than three. Its exact size will depend upon many factors which, in turn, depend upon the ultimate function and use of the oligonucleotide.

The term "primer" as used herein refers to an oligonucleotide, whether occurring naturally as in a purified restriction digest or produced synthetically, which is capable of acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product, which is complementary to a nucleic acid strand, is induced, *i.e.*, in the presence of nucleotides and an inducing agent such as a DNA polymerase and at a suitable temperature and pH. The primer may be either single-stranded or double-stranded and must be sufficiently long to prime the synthesis of the desired extension product in the presence of the inducing agent. The exact length of the primer will

depend upon many factors, including temperature, source of primer and use the method. For example, for diagnostic applications, depending on the complexity of the target sequence, the oligonucleotide primer typically contains 15-25 or more nucleotides, although it may contain fewer nucleotides.

The primers herein are selected to be "substantially" complementary to different strands of a particular target DNA sequence. This means that the primers must be sufficiently complementary to hybridize with their respective strands. Therefore, the primer sequence need not reflect the exact sequence of the template. For example, a non-complementary nucleotide fragment may be attached to the 5' end of the primer, with the remainder of the primer sequence being complementary to the strand. Alternatively, non-complementary bases or longer sequences can be interspersed into the primer, provided that the primer sequence has sufficient complementary with the sequence or hybridize therewith and thereby form the template for the synthesis of the extension product.

As used herein, the terms "restriction endonucleases" and "restriction enzymes" refer to enzymes, each of which cut double-stranded DNA at or near a specific nucleotide sequence.

A cell has been "transformed" by exogenous or heterologous DNA when such DNA has been introduced inside the cell. The transforming DNA may or may not be integrated (covalently

linked) into the genome of the cell. In prokaryotes, yeast, and mammalian cells for example, the transforming DNA may be maintained on an episomal element such as a plasmid. With respect to eukaryotic cells, a stably transformed cell is one in which the transforming DNA has become integrated into a chromosome so that it is inherited by daughter cells through chromosome replication. This stability is demonstrated by the ability of the eukaryotic cell to establish cell lines or clones comprised of a population of daughter cells containing the transforming DNA. A "clone" is a population of cells derived from a single cell or ancestor by mitosis. A "cell line" is a clone of a primary cell that is capable of stable growth *in vitro* for many generations.

Two DNA sequences are "substantially homologous" when at least about 75% (preferably at least about 80%, and most preferably at least about 90% or 95%) of the nucleotides match over the defined length of the DNA sequences. Sequences that are substantially homologous can be identified by comparing the sequences using standard software available in sequence data banks, or in a Southern hybridization experiment under, for example, stringent conditions as defined for that particular system. Defining appropriate hybridization conditions is within the skill of the art. See, *e.g.*, Maniatis et al., *supra*; DNA Cloning, Vols. I & II, *supra*; Nucleic Acid Hybridization, *supra*.

A "heterologous" region of the DNA construct is an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. In another example, coding sequence is a construct where the coding sequence itself is not found in nature (*e.g.*, a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events do not give rise to a heterologous region of DNA as defined herein.

The labels most commonly employed for these studies are radioactive elements, enzymes, chemicals which fluoresce when exposed to ultraviolet light, and others. A number of fluorescent materials are known and can be utilized as labels. These include, for example, fluorescein, rhodamine, auramine, Texas Red, AMCA blue and Lucifer Yellow. A particular detecting material is anti-rabbit antibody prepared in goats and conjugated with fluorescein through an isothiocyanate.

Proteins can also be labeled with a radioactive element or with an enzyme. The radioactive label can be detected by any of the currently available counting procedures. The preferred isotope may

be selected from ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{36}Cl, ^{51}Cr, ^{57}Co, ^{58}Co, ^{59}Fe, ^{90}Y, ^{125}I, ^{131}I, and ^{186}Re.

Enzyme labels are likewise useful, and can be detected by any of the presently utilized colorimetric, spectrophotometric, fluorospectrophotometric, amperometric or gasometric techniques. The enzyme is conjugated to the selected particle by reaction with bridging molecules such as carbodiimides, diisocyanates, glutaraldehyde and the like. Many enzymes which can be used in these procedures are known and can be utilized. The preferred are peroxidase, β-glucuronidase, β-D-glucosidase, β-D-galactosidase, urease, glucose oxidase plus peroxidase and alkaline phosphatase. U.S. Patent Nos. 3,654,090, 3,850,752, and 4,016,043 are referred to by way of example for their disclosure of alternate labeling material and methods.

A particular assay system developed and utilized in the art is known as a receptor assay. In a receptor assay, the material to be assayed is appropriately labeled and then certain cellular test colonies are inoculated with a quantitiy of both the label after which binding studies are conducted to determine the extent to which the labeled material binds to the cell receptors. In this way, differences in affinity between materials can be ascertained.

An assay useful in the art is known as a "cis/trans" assay. Briefly, this assay employs two genetic constructs, one of which is

typically a plasmid that continually expresses a particular receptor of interest when transfected into an appropriate cell line, and the second of which is a plasmid that expresses a reporter such as luciferase, under the control of a receptor/ligand complex. Thus, for example, if it is desired to evaluate a compound as a ligand for a particular receptor, one of the plasmids would be a construct that results in expression of the receptor in the chosen cell line, while the second plasmid would possess a promoter linked to the luciferase gene in which the response element to the particular receptor is inserted. If the compound under test is an agonist for the receptor, the ligand will complex with the receptor, and the resulting complex will bind the response element and initiate transcription of the luciferase gene. The resulting chemiluminescence is then measured photometrically, and dose response curves are obtained and compared to those of known ligands. The foregoing protocol is described in detail in U.S. Patent No. 4,981,784.

As used herein, the term "host" is meant to include not only prokaryotes but also eukaryotes such as yeast, plant and animal cells. A recombinant DNA molecule or gene which encodes a human TADG-16 protein of the present invention can be used to transform a host using any of the techniques commonly known to those of ordinary skill in the art. Especially preferred is the use of a vector containing coding sequences for the gene which encodes a human

TADG-16 protein of the present invention for purposes of prokaryote transformation. Prokaryotic hosts may include *E. coli*, *S. tymphimurium*, *Serratia marcescens* and *Bacillus subtilis*. Eukaryotic hosts include yeasts such as *Pichia pastoris*, mammalian cells and insect cells.

In general, expression vectors containing promoter sequences which facilitate the efficient transcription of the inserted DNA fragment are used in connection with the host. The expression vector typically contains an origin of replication, promoter(s), terminator(s), as well as specific genes which are capable of providing phenotypic selection in transformed cells. The transformed hosts can be fermented and cultured according to means known in the art to achieve optimal cell growth.

The invention includes a substantially pure DNA encoding a TADG-16 protein, a strand of which DNA will hybridize at high stringency to a probe containing a sequence of at least 15 consecutive nucleotides of SEQ ID No. 1. The protein encoded by the DNA of this invention may share at least 80% sequence identity (preferably 85%, more preferably 90%, and most preferably 95%) with the amino acids shown in SEQ ID No. 2. More preferably, the DNA includes the coding sequence of the nucleotides shown in SEQ ID No. 1, or a degenerate variant of such a sequence.

The probe to which the DNA of the invention hybridizes preferably consists of a sequence of at least 20 consecutive nucleotides, more preferably 40 nucleotides, even more preferably 50 nucleotides, and most preferably 100 nucleotides or more (up to 100%) of the coding sequence of the nucleotides shown in SEQ ID No. 1 or the complement thereof. Such a probe is useful for detecting expression of TADG-16 in a cell by a method including the steps of (a) contacting mRNA obtained from the cell with the labeled hybridization probe; and (b) detecting hybridization of the probe with the mRNA.

This invention also includes a substantially pure DNA containing a sequence of at least 15 consecutive nucleotides (preferably 20, more preferably 30, even more preferably 50, and most preferably all) of the region from nucleotides 1 to 3147 of the nucleotides shown in SEQ ID No. 1.

By "high stringency" is meant DNA hybridization and wash conditions characterized by high temperature and low salt concentration, *e.g.*, wash conditions of 65°C at a salt concentration of approximately 0.1 x SSC, or the functional equivalent thereof. For example, high stringency conditions may include hybridization at about 42°C in the presence of about 50% formamide; a first wash at about 65°C with about 2 x SSC containing 1% SDS; followed by a second wash at about 65°C with about 0.1 x SSC.

By "substantially pure DNA" is meant DNA that is not part of a milieu in which the DNA naturally occurs, by virtue of separation (partial or total purification) of some or all of the molecules of that milieu, or by virtue of alteration of sequences that flank the claimed DNA. The term therefore includes, for example, a recombinant DNA which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote; or which exists as a separate molecule (*e.g.*, a cDNA or a genomic or cDNA fragment produced by polymerase chain reaction (PCR) or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequence, *e.g.*, a fusion protein. Also included is a recombinant DNA which includes a portion of the nucleotides shown in SEQ ID No. 1 which encodes an alternative splice variant of TADG-16.

The DNA may have at least about 70% sequence identity to the coding sequence of the nucleotides shown in SEQ ID No. 1, preferably at least 75% (*e.g.*, at least 80%); and most preferably at least 90%. The identity between two sequences is a direct function of the number of matching or identical positions. When a subunit position in both of the two sequences is occupied by the same monomeric subunit, *e.g.*, if a given position is occupied by an adenine in each of two DNA molecules, then they are identical at that

position. For example, if 7 positions in a sequence 10 nucleotides in length are identical to the corresponding positions in a second 10-nucleotide sequence, then the two sequences have 70% sequence identity. The length of comparison sequences will generally be at least 50 nucleotides, preferably at least 60 nucleotides, more preferably at least 75 nucleotides, and most preferably 100 nucleotides. Sequence identity is typically measured using sequence analysis software (*e.g.*, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705).

The present invention is directed towards a vector comprising a DNA sequence which encodes a TADG-16 protein, wherein the vector is capable of replication in a host cell, wherein the vector comprises, in operable linkage: a) an origin of replication; b) a promoter; and c) a DNA sequence coding for the TADG-16 protein. Preferably, the vector of the present invention contains a portion of the DNA sequence shown in SEQ ID No. 1.

A "vector" may be defined as a replicable nucleic acid construct, *e.g.*, a plasmid or viral nucleic acid. Vectors may be used to amplify and/or express nucleic acid encoding TADG-16 protein. An expression vector is a replicable construct in which a nucleic acid sequence encoding a polypeptide is operably linked to suitable control sequences capable of effecting expression of the polypeptide

in a cell. The need for such control sequences will vary depending upon the cell selected and the transformation method chosen. Generally, control sequences include a transcriptional promoter and/or enhancer, suitable mRNA ribosomal binding sites, and sequences which control the termination of transcription and translation.

Methods which are well known to those skilled in the art can be used to construct expression vectors containing appropriate transcriptional and translational control signals. See for example, the techniques described in Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual* (2nd Ed.), Cold Spring Harbor Press, N.Y. A gene and its transcription control sequences are defined as being "operably linked" if the transcription control sequences effectively control the transcription of the gene. Vectors of the invention include, but are not limited to, plasmid vectors and viral vectors. Preferred viral vectors of the invention are those derived from retroviruses, adenovirus, adeno-associated virus, SV40 virus, or herpes viruses.

By a "substantially pure protein" is meant a protein which has been separated from at least some of those components which naturally accompany it. Typically, the protein is substantially pure when it is at least 60%, by weight, free from the proteins and other naturally-occurring organic molecules with which it is naturally

associated *in vivo*. Preferably, the purity of the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight. A substantially pure TADG-16 protein may be obtained, for example, by extraction from a natural source; by expression of a recombinant nucleic acid encoding an TADG-16 polypeptide; or by chemically synthesizing the protein. Purity can be measured by any appropriate method, *e.g.*, column chromatography such as immunoaffinity chromatography using an antibody specific for TADG-16, polyacrylamide gel electrophoresis, or HPLC analysis. A protein is substantially free of naturally associated components when it is separated from at least some of those contaminants which accompany it in its natural state. Thus, a protein which is chemically synthesized or produced in a cellular system different from the cell from which it naturally originates will be, by definition, substantially free from its naturally associated components. Accordingly, substantially pure proteins include eukaryotic proteins synthesized in *E. coli*, other prokaryotes, or any other organism in which they do not naturally occur.

In addition to substantially full-length proteins, the invention also includes fragments (*e.g.*, antigenic fragments) of the TADG-16 protein (SEQ ID No. 2). As used herein, "fragment," as applied to a polypeptide, will ordinarily be at least 10 residues, more typically at least 20 residues, and preferably at least 30 (*e.g.*,

50) residues in length, but less than the entire, intact sequence. Fragments of the TADG-16 protein can be generated by methods known to those skilled in the art, *e.g.*, by enzymatic digestion of naturally occurring or recombinant TADG-16 protein, by recombinant DNA techniques using an expression vector that encodes a defined fragment of TADG-16, or by chemical synthesis. The ability of a candidate fragment to exhibit a characteristic of TADG-16 (*e.g.*, binding to an antibody specific for TADG-16) can be assessed by methods described herein. Purified TADG-16 or antigenic fragments of TADG-16 can be used to generate new antibodies or to test existing antibodies (*e.g.*, as positive controls in a diagnostic assay) by employing standard protocols known to those skilled in the art.

Included in this invention are polyclonal antisera generated by using TADG-16 or a fragment of TADG-16 as the immunogen in, *e.g.*, rabbits. Standard protocols for monoclonal and polyclonal antibody production known to those skilled in this art are employed. The monoclonal antibodies generated by this procedure can be screened for the ability to identify recombinant TADG-16 cDNA clones, and to distinguish them from known cDNA clones.

Further included in this invention are TADG-16 proteins which are encoded at least in part by portions of SEQ ID No. 2, *e.g.*, products of alternative mRNA splicing or alternative protein processing events, or in which a section of TADG-16 sequence has

been deleted. The fragment, or the intact TADG-16 polypeptide, may be covalently linked to another polypeptide, *e.g.*, which acts as a label, a ligand or a means to increase antigenicity.

The invention also includes a polyclonal or monoclonal antibody which specifically binds to TADG-16. The invention encompasses not only an intact monoclonal antibody, but also an immunologically-active antibody fragment, *e.g.*, a Fab or $(Fab)_2$ fragment; an engineered single chain Fv molecule; or a chimeric molecule, *e.g.*, an antibody which contains the binding specificity of one antibody, *e.g.*, of murine origin, and the remaining portions of another antibody, *e.g.*, of human origin.

In one embodiment, the antibody, or a fragment thereof, may be linked to a toxin or to a detectable label, *e.g.*, a radioactive label, non-radioactive isotopic label, fluorescent label, chemiluminescent label, paramagnetic label, enzyme label, or colorimetric label. Examples of suitable toxins include diphtheria toxin, *Pseudomonas* exotoxin A, ricin, and cholera toxin. Examples of suitable enzyme labels include malate hydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, alcohol dehydrogenase, alpha-glycerol phosphate dehydrogenase, triose phosphate isomerase, peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase, acetylcholinesterase, etc.

Examples of suitable radioisotopic labels include ^{3}H, ^{125}I, ^{131}I, ^{32}P, ^{35}S, ^{14}C, etc.

Paramagnetic isotopes for purposes of *in vivo* diagnosis can also be used according to the methods of this invention. There are numerous examples of elements that are useful in magnetic resonance imaging. For discussions on *in vivo* nuclear magnetic resonance imaging, see, for example, Schaefer et al., (1989) *JACC* 14, 472-480; Shreve et al., (1986) *Magn. Reson. Med.* 3, 336-340; Wolf, G. L., (1984) *Physiol. Chem. Phys. Med. NMR* 16, 93-95; Wesbey et al., (1984) *Physiol. Chem. Phys. Med. NMR* 16, 145-155; Runge et al., (1984) *Invest. Radiol.* 19, 408-415. Examples of suitable fluorescent labels include a fluorescein label, an isothiocyalate label, a rhodamine label, a phycoerythrin label, a phycocyanin label, an allophycocyanin label, an ophthaldehyde label, a fluorescamine label, etc. Examples of chemiluminescent labels include a luminal label, an isoluminal label, an aromatic acridinium ester label, an imidazole label, an acridinium salt label, an oxalate ester label, a luciferin label, a luciferase label, an aequorin label, etc.

Those of ordinary skill in the art will know of other suitable labels which may be employed in accordance with the present invention. The binding of these labels to antibodies or fragments thereof can be accomplished using standard techniques commonly known to those of ordinary skill in the art. Typical

techniques are described by Kennedy et al., (1976) *Clin. Chim. Acta* 70, 1-31; and Schurs et al., (1977) *Clin. Chim. Acta* 81, 1-40. Coupling techniques mentioned in the latter are the glutaraldehyde method, the periodate method, the dimaleimide method, the m-maleimidobenzyl-N-hydroxy-succinimide ester method. All of these methods are incorporated by reference herein.

Also within the invention is a method of detecting TADG-16 protein in a biological sample, which includes the steps of contacting the sample with the labeled antibody, *e.g.*, radioactively tagged antibody specific for TADG-16, and determining whether the antibody binds to a component of the sample.

As described herein, the invention provides a number of diagnostic advantages and uses. For example, the TADG-16 protein is useful in diagnosing cancer in different tissues since this protein is highly overexpressed in tumor cells. Antibodies (or antigen-binding fragments thereof) which bind to an epitope specific for TADG-16, are useful in a method of detecting TADG-16 protein in a biological sample for diagnosis of cancerous or neoplastic transformation. This method includes the steps of obtaining a biological sample (*e.g.*, cells, blood, plasma, tissue, etc.) from a patient suspected of having cancer, contacting the sample with a labeled antibody (*e.g.*, radioactively tagged antibody) specific for TADG-16, and detecting the TADG-16 protein using standard immunoassay techniques such as

an ELISA. Antibody binding to the biological sample indicates that the sample contains a component which specifically binds to an epitope within TADG-16.

Likewise, a standard Northern blot assay can be used to ascertain the relative amounts of TADG-16 mRNA in a cell or tissue obtained from a patient suspected of having cancer, in accordance with conventional Northern hybridization techniques known to those of ordinary skill in the art. This Northern assay uses a hybridization probe, *e.g.*, radiolabelled TADG-16 cDNA, either containing the full-length, single stranded DNA having a sequence complementary to SEQ ID No. 1, or a fragment of that DNA sequence at least 20 (preferably at least 30, more preferably at least 50, and most preferably at least 100) consecutive nucleotides in length. The DNA hybridization probe can be labeled by any of the many different methods known to those skilled in this art.

Antibodies to the TADG-16 protein can be used in an immunoassay to detect increased levels of TADG-16 protein expression in tissues suspected of neoplastic transformation. These same uses can be achieved with Northern blot assays and analyses.

The TADG-16 cDNA is 1129 base pairs long (SEQ ID No. 1) encoding for a 314 amino acid protein (SEQ ID No. 2). The availability of the TADG-16 gene provides numerous utilities. For example, the TADG-16 gene can be used as a diagnostic or therapeutic target in

ovarian and other carcinomas, including breast, prostate, lung and colon.

The present invention is directed to DNA encoding a tumor antigen-derived gene (TADG-16) protein, selected from (a) an isolated DNA which encodes a TADG-16 protein; (b) an isolated DNA which hybridizes under high stringency conditions to the isolated DNA of (a) above and which encodes a TADG-16 protein; and (c) an isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein. It is preferred that the DNA has the sequence shown in SEQ ID No. 1 and the TADG-16 protein has the amino acid sequence shown in SEQ ID No. 2.

The present invention is directed toward a vector comprising the TADG-16 DNA and regulatory elements necessary for expression of the DNA in a cell, or a vector in which the TADG-16 DNA is positioned in reverse orientation relative to the regulatory elements such that TADG-16 antisense mRNA is produced. An antisense molecule corresponding to TADG-16 mRNA is shown in SEQ ID No. 16. The invention is also directed toward host cells transfected with either of the above-described vector(s). Representative host cells are bacterial cells, mammalian cells, plant cells and insect cells. Preferably, the bacterial cell is *E. coli.*

The present invention is directed toward an isolated and purified TADG-16 protein coded for by DNA selected from the following: (a) an isolated DNA which encodes a TADG-16 protein; (b) an isolated DNA which hybridizes under high stringency conditions to isolated DNA of (a) above and which encodes a TADG-16 protein; and (c) an isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein. Preferably, the protein has the amino acid sequence shown in SEQ ID No. 2.

The present invention is directed toward a method for detecting TADG-16 mRNA in a sample, comprising the steps of (a) contacting a sample with a probe which is specific for TADG-16; and (b) detecting binding of the probe to TADG-16 mRNA in the sample. The present invention is also directed toward a method of detecting TADG-16 protein in a sample, comprising the steps of (a) contacting a sample with an antibody which is specific for TADG-16 or a fragment thereof; and (b) detecting binding of the antibody to TADG-16 protein in the sample. Generally, the sample is a biological sample; preferably, the biological sample is from an individual; and typically, the individual is suspected of having cancer.

The present invention is directed toward a kit for detecting TADG-16 mRNA, comprising an oligonucleotide probe, wherein the probe is specific for TADG-16. The kit may further comprise a label

with which to label the probe; and means for detecting the label. The present invention is additionally directed toward a kit for detecting TADG-16 protein, comprising an antibody which is specific for TADG-16 protein or a fragment thereof. The kit may further comprise means to detect the antibody.

The present invention is directed toward a antibody which is specific for TADG-16 protein or a fragment thereof.

The present invention is directed toward a method of screening for compounds that inhibit TADG-16, comprising the steps of: (a) contacting a sample containing TADG-16 protein with a compound; and (b) assaying for TADG-16 protease activity. Typically, a decrease in the TADG-16 protease activity in the presence of the compound relative to TADG-16 protease activity in the absence of the compound is indicative of a compound that inhibits TADG-16.

The present invention is directed toward a method of inhibiting expression of TADG-16 in a cell, comprising the step of: (a) introducing a vector expressing TADG-16 antisense mRNA into a cell which hybridizes to endogenous TADG-16 mRNA, thereby inhibiting expression of TADG-16 in the cell. Generally, the inhibition of TADG-16 expression is for treating cancer.

The present invention is directed toward a method of inhibiting a TADG-16 protein in a cell, comprising the step of (a) introducing an antibody specific for a TADG-16 protein or a fragment

thereof into a cell which inhibits the TADG-16 protein. Generally, the inhibition of the TADG-16 protein is for treating cancer.

The present invention is directed toward a method of targeted therapy to an individual, comprising the step of (a) administering a compound having a targeting moiety and a therapeutic moiety to an individual, wherein the targeting moiety is specific for TADG-16. Representative targeting moiety are an antibody specific for TADG-16, a ligand that binds TADG-16 or a ligand binding domain of TADG-16, *e.g.*, a CUB domain, an LDLR domain, etc. Likewise, a representative therapeutic moiety is a radioisotope, a toxin, a chemotherapeutic agent, an immune stimulant or a cytotoxic agent. Typically, the above-described method is useful when the individual suffers from ovarian cancer, breast cancer, lung cancer, prostate cancer, colon cancer or other cancers in which TADG-16 is overexpressed.

The present invention is directed toward a method of diagnosing cancer in an individual, comprising the steps of (a) obtaining a biological sample from an individual; and (b) detecting TADG-16 in the sample. Generally, the presence of TADG-16 in the sample is indicative of the presence of carcinoma in the individual, and the absence of TADG-16 in the sample is indicative of the absence of carcinoma in the individual. Typically, the biological sample is blood, urine, saliva tears, interstitial fluid, ascites fliud, tumor tissue

biopsy or circulating tumor cells. Representative means of detecting TADG-16 are by Northern blot, Western blot, PCR, dot blot, ELIZA sandwich assay, radioimmunoassay, DNA array chips or flow cytometry (after labeling tumor cells). This method may be useful in diagnosing cancers such as ovarian, breast, lung, colon, prostate and others with increased TADG-16 expression.

The present invention is also directed to an antisense oligonucleotide having the nucleotide sequence complementary to a TADG-16 mRNA sequence. The present invention is also directed to a composition comprising such an antisense oligonucleotide and a physiologically acceptable carrier therefore.

The present invention is also directed to a method of treating a neoplastic state in an individual in need of such treatment, comprising the step of administering to said individual an effective dose of an antisense oligonucleotide. Preferably, the neoplastic state is ovarian cancer, breast cancer and other cancers that exhibit TADG-16 overexpression. For such therapy, the oligonucleotides alone or in combination with other anti-neoplastic agents can be formulated for a variety of modes of administration, including systemic, topical or localized administration. Techniques and formulations generally can be found in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA). The oligonucleotide active ingredient is generally combined with a pharamceutically accceptable carrier such as a

diluent or excipient which can include fillers, extenders, binders, wetting agents, disintergrants, surface active agents or lubricants, depending on the nature of the mode of administration and dosage forms. Typical dosage forms include tablets, powders, liquid preparations including suspensions, emulsions, and solutions, granules, capsules and suppositories, as well as liquid preparations for injections, including liposome preparations.

For systemic administration, injection is preferred, including intramuscular, intravenous, intraperitoneal and subcutaneous. For injection, the oligonucleotides of the invention are formulated in liquid solutions, preferably in physiologically compatible buffers. In addition, the oligonucleotides can be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms are also incldued. Dosages that can be used for systemic administration preferably range from about 0.01 mg/kg to 50 mg/kg administered once or twice per day. However, different dosing schedules can be utilized depending on (1) the potency of an individual oligonucleotide at inhibiting the activity of its target DNA, (2) the severity or extent of the pathological disease state, or (3) the pharmacokinetic behavior of a given oligonucleotide.

The present invention is directed toward a method of vaccinating an individual against TADG-16, comprising the steps of (a) inoculating an individual with a TADG-16 protein or fragment thereof

which lacks TADG-16 protease activity. The inoculation with the TADG-16 protein or fragment thereof elicits an immune response in the individual, thereby vaccinating the individual against TADG-16. The vaccination with TADG-16 described herein is intended for an individual who has cancer, is suspected of having cancer or is at risk of getting cancer. The present invention is also directed toward an immunogenic composition, comprising an immunogenic fragment of TADG-16 and an appropriate adjuvant. Generally, the TADG-16 fragment useful for vaccinating an individual consists of a 9-residue fragment up to and including a 20-residue fragment. Preferably, the 9-residue fragments have a sequence such as SEQ ID Nos. 17, 18, 19, 77, 78, 79, 80, 97, 98, 99, 137, 138, 139, 140 or 141. Other TADG-16 fragment useful for vaccinating an individual may be readily determined by an individual having ordinary skill in this art using routine techniques.

The present invention is further directed to a method of regulating the expression of the TADG-16 protein by designing antisense oligonucleotides directed to the DNA encoding the TADG-16 protein. A person having ordinary skill in this art would be able design such antisense oligonucleotides without undue experimentation.

The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any fashion.

EXAMPLE 1

Cloning of the TADG-16 catalytic domain

Using WISH (an amnion derived cell line) cDNA (ATCC) as a template for PCR with degenerate primers designed to the conserved regions surrounding the invariant histidine and serine residues of the catalytic triad of the serine protease family of proteins, a 498 base pair product was obtained that was similar in particular consensus sequences to other known serine proteases (Figure 1).

The sequences of the degenerate primers used in the initial PCR are as follows:

Serp-S (Sense): 5'-TGGGTIGTIACIGCIGCICA(CT)TG-3' (SEQ ID No. 8); and

Serp-S (Antisense): 5'-A(AG)IGGICCICCI(CG)(TA)(AG)TCICC-3' (SEQ ID No. 9).

Reactions were carried out as described by Underwood et al. (*Cancer Res.*, 59, 4435-9 (1999)).

EXAMPLE 2

Detection of TADG-16 mRNA

Using the radioactively labeled catalytic domain as a probe, Northern blot analysis of multiple human tissues revealed that TADG-16 is highly expressed in normal human testes and in some ovarian tumors, but not detectable at significant levels in other tissues examined (Figure 2). More importantly, Northern analysis showed that the TADG-16 transcript is approximately 1.4 kilobases in length.

EXAMPLE 3

Sequence analysis of TADG-16

Comparison of the TADG-16 catalytic domain to the EST database identified a homologous sequence (Accession No. AA620757) that overlapped a portion of the TADG-16 catalytic domain clone and also included the 3'-untranslated region and poly (A) tail of the TADG-16 transcript (Figure 3). Comparison of the catalytic domain clone to the GenBank non-redundant database identified a genomic cosmid clone (Accession No. AC005361) homologous to the catalytic domain clone. Using the GRAIL exon identification program available through the National Center for

Biotechnology Information, potential exons encoding the 5' portion of the TADG-16 transcript were identified.

EXAMPLE 4

Cloning of the TADG-16 cDNA

A sense PCR primer (T16-F1: 5'-GTCAGGCCGCGGGAGAGGAG-3' (SEQ ID No. 10)) was designed to the cDNA predicted by the Grail program and used in conjunction with an antisense primer (T16-R2: 5'-ACTCTGGGCCATCAGCTTCT-3' (SEQ ID No. 11)) designed to the overlapping EST that included the polyA$^+$ tail (GenBank Accession No. AA620757 encoding bases 614 to 1129 of TADG-16). Additional antisense primers were utilized in 5'-RACE experiments using a human testes cDNA library as template to identify the 40-most 5' bases. The sequence of the 5'-RACE primers are as follows:

T16-R6: 5'-CGGAGGGATCACTAAGGTCACTATACGT-3' (SEQ ID No. 12); and

T16-R7: 5'-TATACGTTTCAAAGCAGTGCGCCGCCGT-3' (SEQ ID No. 13).

This allowed for the identification of the 1129 bases of the sequence reported herein. Within this 1129 bases, there is a Kozak's consensus

sequence for the initiation of translation, an open reading frame encoding a 314 amino acid protein and a polyadenylation signal.

EXAMPLE 5

Tissue-specific expression of TADG-16

Using a previously authenticated semi-quantitative PCR technique (Shigemasa et al., *J. Soc. Gynecological Inv.*, 4, 95-102 (1997)), the expression level of the TADG-16 transcript was examined in normal ovarian tissue and ovarian tumor specimens. To do this, a TADG-16-specific PCR product was co-amplified with a PCR product for β-tubulin as an internal control. To amplify a 237 bp PCR product specific for TADG-16, the following primers were used:

T16-F2: 5'-GGTCGCCATCATAAACAACT-3' (SEQ ID No. 14); and

T16-R2: 5'-ACTCTGGGCCATCAGCTTCT-3' (SEQ ID No. 15).

The reaction mixture was heated to 94°C for 1.5 min, then 30 cycles of PCR was carried out under the following conditions: 30 sec of denaturation at 94°C, 30 sec of annealing at 62°C and 30 sec of extension at 72°C. A final extension at 72°C was performed for 7 min before the reaction was terminated. These PCR products were electrophoresed through an agarose gel to separate them based on

size. Based on this experiment, TADG-16 appears to be expressed in tumor tissue (Figures 5 & 6).

EXAMPLE 6

Expression of TADG-16 in tumors

The expression of the serine protease TADG-16 gene in normal, low malignant potential tumors, and carcinoma (both mucinous and serous type) by quantitative PCR using TADG-16-specific primers was determined (primers directed toward the β-tubulin message were used as an internal standard). These data confirm the overexpression of the TADG-16 surface protease gene in ovarian carcinoma, including both low malignant potential tumors and overt carcinoma. Expression of TADG-16 is increased over normal levels in low malignant potential tumors, and high stage tumors (Stage III) of this group have higher expression of TADG-16 when compared to low stage tumors (Stage 1) (Table 3). In overt carcinoma, serous tumors exhibit the highest levels of TADG-16 expression, while mucinous tumors express levels of TADG-16 comparable with the high stage low malignant potential group.

TABLE 3

Expression of TADG-16

Case No.	Code	Stage	Grade	Histology	TADG-16
1	1	-	-	-	0.553
2	1	-	-	-	0.232
3	1	-	-	-	0.229
4	1	-	-	-	0.400
5	1	-	-	-	0.226
6	1	-	-	-	0.230
7	1	-	-	-	0.269
8	2	-	-	-	0.121
9	2	-	-	-	0.514
10	2	-	-	-	0.333
11	2	-	-	-	0.323
12	3				0.732
13	3				0.487
14	3				0.850
15	4	1	1	2	0.815
16	4	1	1	3	0.287
17	4	1	2	2	0.382
18	4	1	1	1	0.400
19	4	1	1	2	0.548
20	4	1	2	4	2.120
21	4	1	2	4	1.700
22	4	1	1	1	1.760
23	4	1	2	1	1.240
24	4	2	3	1	1.320
25	4	2	1	1	0.710
26	4	3	1	2	0.828
27	4	3	1	1	1.730
28	4	3	1	1	0.510
29	4	3	1	1	2.320
30	4	3	1	2	0.792
31	4	3	1	3	0.899
32	4	3	2	1	1.880
33	4	3	2	1	1.130
34	4	3	2	3	0.892
35	4	3	2	3	1.990
36	4	3	2	3	0.365
37	4	3	3	1	1.840
38	4	3	3	1	1.430
39	4	3	3	3	0.830
40	4	3	1	1	1.730
41	4	3	1	1	2.910

Code: 1, normal ovary; 2, benign tumor (adenoma); 3, LMP tumor; 4, cancer (adenocarcinoma).
Stage = Clinical stage: 1, stage 1; 2, stage 2; 3, stage 3.
Grade = Histological grade: 1, grade 1; 2, grade 2; 3, grade 3.
Histology: 1, serous carcinoma; 2, mucinous carcinoma; 3, endometrioid carcinoma; 4, clear cell carcinoma.

TABLE 4

mRNA Expression Levels of TADG-16 Gene in Ovarian Cancers

	N	mRNA Expression Levels mean	SD
Normal ovary	7	0.306	0.126
Benign tumor	4	0.323	0.161
LMP tumor	3	0.690	0.185
Ovarian cancer	27	1.235	0.692
Clinical stage			
Stage 1	9	1.028	0.695
Stage 2	2	1.015	0.431
Stage 3	16	1.380	0.711
Histological grade			
Grade 1	14	1.160	0.794
Grade 2	9	1.300	0.667
Grade 3	4	1.355	0.415
Histological type			
Serous	14	1.494	0.688
Mucinous	5	0.673	0.199
Endometrioid	6	0.877	0.609
Clear Cell	2	1.910	0.297

TABLE 5

	p-value (unpaired *t*-test)
Tumor type	
normal vs. benign	0.8473
normal vs. LMP	0.0046
normal vs. cancer	0.0014
benign vs. LMP	0.0375
benign vs. cancer	0.0148
LMP vs. cancer	0.1905
Stage	
stage 1 vs. stage 2	0.9808
stage 1 vs. stage 3	0.2435
stage 2 vs. stage 3	0.4951
Grade	
grade 1 vs. grade 2	0.6659
grade 1 vs. grade 3	0.6472
grade 2 vs. grade 3	0.8830
Histology	
serous vs. mucinous	0.0192
serous vs. endometrioid	0.0743
serous vs. clear cell	0.4230
mucinous vs. endometrioid	0.4937
mucinous vs. clear cell	0.0012
endometrioid vs. clear cell	0.0678

EXAMPLE 7

Antisense TADG-16

TADG-16 is cloned and expressed in the opposite orientation such that an antisense RNA molecule (SEQ ID No. 16) is produced. For example, the antisense RNA is used to hybridize to the

complementary RNA in the cell and thereby inhibit translation of TADG-16 RNA into protein.

EXAMPLE 8

Peptide ranking

For vaccine or immune stimulation, individual 9-mers to 11-mers of the TADG-16 protein were examined to rank the binding of individual peptides to the top 8 haplotypes in the general population (Parker et al., (1994)). The computer program used for this analyses can be found at <http://www-bimas.dcrt.nih.gov/molbio/hla_bind/>. Table 6 shows the peptide ranking based upon the predicted half-life of each peptide's binding to a particular HLA allele. A larger half-life indicates a stronger association with that peptide and the particular HLA molecule. The TADG-16 peptides that strongly bind to an HLA allele are putative immunogens, and are used to innoculate an individual against hepsin.

TABLE 6

TADG-16 peptide ranking

HLA Type & Ranking	Start	Peptide	Predicted Dissociation$_{1/2}$	SEQ ID No.
HLA A0201				
1	70	SLLSHRWAL	592.807	17
2	299	LLFFPLLWA	395.296	18
3	142	KLSAPVTYT	329.937	19
4	96	WMVQFGQLT	94.077	20
5	10	ALLLARAGL	79.041	21
6	252	QIGVVSWGV	71.726	22
7	248	GLWYQIGVV	70.769	23
8	139	ALVKLSAPV	69.552	24
9	291	SQPDPSWPL	66.602	25
10	130	YLGNSPYDI	47.991	26
11	190	TLQEVQVAI	42.774	27
12	6	ALLLALLLA	42.278	28
13	165	FENRTDCWV	34.216	29
14	71	LLSHRWALT	21.536	30
15	8	LLALLLARA	19.425	31
16	297	WPLLFFPLL	17.136	32
17	113	QAYYTRYFV	17.002	33
18	123	NIYLSPRYL	10.339	34
19	104	TSMPSFWSL	7.352	
35				
20	273	NISHHFEWI	7.345	
36				
HLA A0205				
1	70	SLLSHRWAL	25.200	37
2	42	IVGGEDAEL	23.800	38
3	10	ALLLARAGL	21.000	39
4	291	SQPDPSWPL	20.160	40
5	297	WPLLFFPLL	12.600	41
6	248	GLWYQIGVV	12.000	42
7	82	HCFETYSDL	6.300	43

	8	142	KLSAPVTYT	[illegible]00	44
	9	96	WMVQFGQLT	[illegible]00	45
	10	299	LLFFPLLWA	5.100	46
	11	303	PLLWALPLL	4.200	47
	12	123	NIYLSPRYL	4.200	48
	13	98	VQFGQLTSM	4.080	49
	14	306	WALPLLGPV	3.600	50
	15	71	LLSHRWALT	3.400	51
	16	53	WPWQGSLRL	3.150	52
	17	302	FPLLWALPL	3.150	53
	18	130	YLGNSPYDI	3.000	54
	19	6	ALLLALLLA	3.000	55
	20	190	TLQEVQVAI	3.000	56
HLA A1					
	1	44	GGEDAELGR	11.250	57
	2	90	LSDPSGWMV	7.500	58
	3	143	LSAPVTYTK	6.000	59
	4	292	QPDPSWPLL	2.500	60
	5	203	MCNHLFLKY	2.500	61
	6	87	YSDLSDPSG	1.500	62
	7	168	RTDCWVTGW	1.250	63
	8	47	DAELGRWPW	0.900	64
	9	23	SQEAAPLSG	0.675	65
	10	7	LLLALLLAR	0.500	66
	11	157	CLQASTFEF	0.500	67
	12	202	SMCNHLFLK	0.500	68
	13	111	SLQAYYTRY	0.500	69
	14	125	YLSPRYLGN	0.500	70
	15	152	HIQPICLQA	0.500	71
	16	79	TAAHCFETY	0.500	72
	17	238	SGGPLACNK	0.500	73
	18	172	WVTGWGYIK	0.400	74
	19	110	WSLQAYYTR	0.300	75
	20	191	LQEVQVAII	0.270	76
HLA A24					
	1	118	RYFVSNIYL	400.000	77
	2	177	GYIKEDEAL	300.000	78
	3	210	KYSFRKDIF	140.000	79
	4	270	VYTNISHHF	60.000	80
	5	148	TYTKHIQPI	28.800	81
	6	300	LFFPLLWAL	24.000	82
	7	234	CFGDSGGPL	22.000	83
	8	135	PYDIALVKL	9.600	84

9	4	RGALLLALL	[illegible]	85
10	104	TSMPSFWSL	8.640	86
11	296	SWPLLFFPL	7.500	87
12	250	WYQIGVVSW	7.200	88
13	5	GALLLALLL	7.200	89
14	95	GWMVQFGQL	7.200	90
15	199	INNSMCNHL	7.200	91
16	297	WPLLFFPLL	7.200	92
17	291	WQPDPSWPL	7.200	93
18	183	EALPSPHTL	7.200	94
19	86	TYSDLSDPS	7.200	95
20	10	ALLLARAGL	6.000	96

HLA B7

1	297	WPLLFFPLL	80.000	97
2	302	FPLLWALPL	80.000	98
3	53	WPWQGSLRL	80.000	99
4	292	QPDPSWPLL	24.000	100
5	145	APVTYTKHI	24.000	101
6	42	IVGGEDAEL	20.000	102
7	10	ALLLARAGL	18.000	103
8	104	TSMPSFWSL	12.000	104
9	183	EALPSPHTL	12.000	105
10	201	NSMCNHLFL	12.000	106
11	5	GALLLALLL	12.000	107
12	291	SQPDPSWPL	6.000	108
13	70	SLLSHRWAL	6.000	109
14	195	QVAIINNSM	5.000	110
15	116	YTRYFVSNI	4.000	111
16	199	INNSMCNHL	4.000	112
17	82	HCFETYSDL	4.000	113
18	132	GNSPYDIAL	4.000	114
19	1	MGARGALLL	4.000	115
20	63	DSHVCGVSL	4.000	116

HLA B8

1	183	EALPSPHTL	1.600	117
2	58	SLRLWDSHV	1.200	118
3	82	HCFETYSDL	1.200	119
4	116	YTRYFVSNI	1.000	120
5	2	GARGALLLA	0.800	121
6	302	FPLLWALPL	0.800	122
7	53	WPWQGSLRL	0.800	123
8	31	GPCGRRVIT	0.800	124
9	297	WPLLFFPLL	0.800	125

	10	5	GALLLALLL	[illegible]800	126
	11	71	LLSHRWALT	[illegible]400	127
	12	242	LACNKNGLW	0.400	128
	13	10	ALLLARAGL	0.400	129
	14	70	SLLSHRWAL	0.400	130
	15	63	DSHVCGVSL	0.400	131
	16	89	DLSDPSGWM	0.300	132
	17	132	GNSPYDIAL	0.200	133
	18	140	LVKLSAPVT	0.200	134
	19	149	YTKHIQPIC	0.200	135
	20	15	RAGLRKPES	0.200	136
HLA B2702					
	1	117	GRWPWQVSL	1000.000	137
	2	51	LRSDQEPLY	300.00	138
	3	263	RRKLPVDRI	200.000	139
	4	74	SRWRVFAGA	100.000	140
	5	128	GRDTSLGRW	100.000	141
	6	266	WRLCGIVSW	60.000	142
	7	3	LRYDGAHLC	60.000	143
	8	34	LRALTHSEL	60.000	144
	9	213	FREWIFQAI	20.000	145
	10	18	GRLPHTQRL	20.000	146
	11	101	ERNRVLSRW	20.000	147
	12	227	NRVLSRWRV	20.000	148
	13	59	SRPKVAALT	20.000	149
	14	40	VRTAGANGT	20.000	150
	15	35	QRLLEVISV	18.000	151
	16	98	CQGDSGGPF	10.000	152
	17	112	ARLMVFDKT	6.000	153
	18	291	WRVFAGAVA	6.000	154
	19	191	GRFLAAICQ	6.000	155
	20	157	CLQASTFEF	3.000	156
HLA B4403					
	1	122	SNIYLSPRY	30.000	157
	2	182	DEALPSPHT	24.000	158
	3	45	GEDAELGRW	18.000	159
	4	136	YDIALVKLS	11.250	160
	5	170	DCWVTGWGY	9.000	161
	6	243	ACNKNGLWY	6.000	162
	7	163	FEFENRTDC	6.000	163
	8	88	SDLSDPSGW	6.000	164
	9	79	TAAHCFETY	6.000	165
	10	278	FEWIQKLMA	6.000	166

11	192	QEVQVAIIN	[illegible]00	167
12	92	DPSGWMVQF	4.500	168
13	294	DPSWPLLFF	4.500	169
14	203	MCNHLFLKY	4.500	170
15	76	WALTAAHCF	4.500	171
16	165	FENRTDCWV	4.000	172
17	215	KDIFGDMVC	2.500	173
18	48	AELGRWPWQ	2.400	174
19	272	TNISHHFEW	2.250	175
20	227	AQGGKDACF	2.250	176

Implications

That TADG-16 is found at low levels in some normal tissues may not detract from it's potential usefulness as a tumor marker, as there may be an aberrant expression pattern at the translational level that, *e.g.*, allows for detection of TADG-16 in tumor patients but not in healthy patients, and/or activation of the TADG-16 enzyme may be necessary for tumor progression. In the case of the serine protease hepsin, Torres-Rosada et al. demonstrated by down-regulating hepsin that hepsin was required for growth of certain mammalian cells in culture.

The TADG-16 protein sequence is 314 amino acids in length and contains a secretion signal sequence, which suggests that this protein is functional in an extracellular capacity. A proteolytic cleavage site usually associated with protease enzyme activation is present downstream from the secretion signal sequence between

amino acid residues 19 and 20. Moreover, the identified clone contains the necessary amino acids characteristic of a functional serine protease catalytic triad, thereby suggesting that this protein may be functioning in a manner that would promote cellular growth or expansion.

Any patents or publications mentioned in this specification are indicative of the levels of those skilled in the art to which the invention pertains. These patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The present examples along with the methods, procedures, treatments, molecules, and specific compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention as defined by the scope of the claims.

WHAT IS CLAIMED IS:

1. DNA encoding a tumor antigen-derived gene (TADG-16) protein, selected from the group consisting of:

(a) isolated DNA which encodes a TADG-16 protein;

(b) isolated DNA which hybridizes under high stringency conditions to the isolated DNA of (a) above and which encodes a TADG-16 protein; and

(c) isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein.

2. The DNA of claim 1, wherein said DNA has the sequence shown in SEQ ID No. 1.

3. The DNA of claim 1, wherein said TADG-16 protein has the amino acid sequence shown in SEQ ID No. 2.

4. An oligonucleotide having the nucleotide sequence complementary to a sequence of claim 1.

5. A composition comprising the oligonucleotide according to claim 4 and a physiologically acceptable carrier therefore.

6. A vector comprising the DNA of claim 1 and regulatory elements necessary for expression of said DNA in a cell.

7. The vector of claim 6, wherein said DNA encodes a TADG-16 protein having the amino acid sequence shown in SEQ ID No. 2.

8. The vector of claim 6, wherein said DNA is positioned in reverse orientation relative to said regulatory elements such that TADG-16 antisense mRNA is produced.

9. A host cell transfected with the vector of claim 6 said vector expressing a TADG-16 protein.

10. The host cell of claim 9, wherein said cell is selected from the group consisting of bacterial cells, mammalian cells, plant cells and insect cells.

11. The host cell of claim 10, wherein said bacterial cell is *E. coli*.

12. Isolated and purified TADG-16 protein coded for by DNA selected from the group consisting of:

(a) isolated DNA which encodes a TADG-16 protein;

(b) isolated DNA which hybridizes under high stringency conditions to isolated DNA of (a) above and which encodes a TADG-16 protein; and

(c) isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein.

13. The TADG-16 protein of claim 12, wherein said protein has the amino acid sequence shown in SEQ ID No. 2.

14. An antibody, wherein said antibody is specific for TADG-16 protein or a fragment thereof.

15. A method for detecting TADG-16 mRNA in a sample, comprising the steps of:

(a) contacting a sample with a probe, wherein said probe is specific for TADG-16; and

(b) detecting binding of said probe to TADG-16 mRNA in said sample.

16. The method of claim 15, wherein said sample is a biological sample.

17. The method of claim 16, wherein said biological sample is from an individual.

18. The method of claim 17, wherein said individual is suspected of having cancer.

19. A kit for detecting TADG-16 mRNA, comprising:

an oligonucleotide probe, wherein said probe is specific for TADG-16.

20. The kit of claim 19, further comprising:

a label with which to label said probe; and

means for detecting said label.

21. A method of detecting TADG-16 protein in a sample, comprising the steps of:

(a) contacting a sample with an antibody, wherein said antibody is specific for TADG-16 or a fragment thereof; and

(b) detecting binding of said antibody to TADG-16 protein in said sample.

22. The method of claim 21, wherein said sample is a biological sample.

23. The method of claim 22, wherein said biological sample is from an individual.

24. The method of claim 23, wherein said individual is suspected of having cancer.

25. A kit for detecting TADG-16 protein, comprising:

an antibody, wherein said antibody is specific for TADG-16 protein or a fragment thereof.

26. The kit of claim 25, further comprising:

means to detect said antibody.

27. A method of inhibiting endogenous expression of TADG-16 in a cell, comprising the step of:

(a) introducing the vector of claim 8 into a cell, wherein expression of said vector produces TADG-16 antisense mRNA in said cell, wherein said TADG-16 antisense mRNA hybridizes to endogenous

TADG-16 mRNA thereby inhibiting endogenous expression of TADG-16 in said cell.

28. A method of inhibiting a TADG-16 protein in a cell, comprising the step of:

introducing an antibody into a cell, wherein said antibody is specific for a TADG-16 protein or a fragment thereof, wherein binding of said antibody to said TADG-16 protein inhibits said TADG-16 protein.

29. A method of treating a neoplastic state in an individual in need of such treatment, comprising the step of administering to said individual an effective dose of the oligonucleotide of claim 4.

30. The method of claim 29, wherein said neoplastic state is selected from the group consisting of ovarian cancer, breast cancer, lung cancer, colon cancer and prostate cancer.

31. A method of vaccinating an individual against TADG-16, comprising the steps of:

inoculating an individual with a TADG-16 protein or fragment thereof, wherein said TADG-16 protein or fragment thereof lack TADG-16 protease activity, wherein said inoculation with said TADG-16 protein or fragment thereof elicits an immune response in said individual, thereby vaccinating said individual against TADG-16.

32. The method of claim 31, wherein said TADG-16 fragment is selected from the group consisting of a 9-residue fragment up to a 20-residue fragment.

33. The method of claim 32, wherein said 9-residue fragment is selected from the group consisting of SEQ ID Nos. 17, 18, 19, 77, 78, 79, 80, 97, 98, 99, 137, 138, 139, 140 and 141.

34. The method of claim 31, wherein said individual has cancer, is suspected of having cancer or is at risk of getting cancer.

35. An immunogenic composition, comprising an immunogenic fragment of a TADG-16 protein and an adjuvant.

36. The immunogenic composition of claim 35, wherein said fragment is selected from the group consisting of a 9-residue fragment up to a 20-residue fragment.

37. The immunogenic composition of claim 36, wherein said 9-residue fragment is selected from the group consisting of SEQ ID Nos. 17, 18, 19, 77, 78, 79, 80, 97, 98, 99, 137, 138, 139, 140 and 141.

38. A method of diagnosing cancer in an individual, comprising the steps of:

(a) obtaining a biological sample from an individual;

(b) detecting TADG-16 in said sample, wherein the presence of TADG-16 in said sample is indicative of the presence of carcinoma in said individual, wherein the absence of TADG-16 in said sample is indicative of the absence of carcinoma in said individual.

39. The method of claim 38, wherein said biological sample is selected from the group consisting of blood, urine, saliva, tears, interstitial

40. The method of claim 38, wherein said detection of said TADG-16 is by means selected from the group consisting of Northern blot, Western blot, PCR, dot blot, ELIZA sandwich assay, radioimmunoassay, DNA array chips and flow cytometry of tumor cells, wherein said tumor cells are labeled.

41. The method of claim 38, wherein said carcinoma is selected from the group consisting of ovarian, breast, lung, colon, prostate and other in which TADG-16 is overexpressed.

42. A method of screening for compounds that inhibit TADG-16, comprising the steps of:

(a) contacting a sample with a compound, wherein said sample comprises TADG-16 protein; and

(b) assaying for TADG-16 protease activity, wherein a decrease in said TADG-16 protease activity in the presence of said compound relative to TADG-16 protease activity in the absence of said compound is indicative of a compound that inhibits TADG-16.

43. A method of targeted therapy to an individual, comprising the step of:

administering a compound to an individual, wherein said compound has a targeting moiety and a therapeutic moiety, wherein said targeting moiety is specific for TADG-16.

44. The method of claim 43, wherein said targeting moiety is selected from the group consisting of an antibody specific for TADG-16 and a ligand that binds TADG-16 or a ligand binding domain thereof.

45. The method of claim 43, wherein said therapeutic moiety is selected from the group consisting of a radioisotope, a toxin, a chemotherapeutic agent, an immune stimulant and a cytotoxic agent.

46. The method of claim 43, wherein said individual suffers from a cancer selected from the group consisting of ovarian, lung, prostate, colon and others in which TADG-16 is overexpressed.

```
         1                                                    50
Prom     ---------- ---------- ---------- ---------- ----------
Tryl     ---------- ---------- ---------- ---------- ----------
Scce     ---------- ---------- ---------- ---------- ----------
Heps     XXXXMAQKEG GRTVPCCSRP KVAALTAGTL LLLTAIGAAS WAIVAVLLRS
Tadg16   ---------- ---------- ---------- ---------- ----------

         51                                                  100
Prom     ---------- ---------- ---------- ---------- ----------
Tryl     ---------- ---------- ---------- ---------- ----------
Scce     ---------- ---------- ---------- ---------- ----------
Heps     DQEPLYPVQV SSADARLMVF DKTEGTWRLL CSSRSNARVA GLSCEEMGFL
Tadg16   ---------- ---------- ---------- ---------- ----------

         101                                                 150
Prom     ---------- ---------- ---------- ---------- --MKKLMVVL
Tryl     ---------- ---------- ---------- ---------- --MNPLL.IL
Scce     ---------- ---------- ---------- -------MAR SLLLPLQILL
Heps     RALTHSELDV RTAGANGTSG FFCVDEGRLP HTQRLLEVIS VCDCPRGRFL
Tadg16   ---------- ---------- ---------- -MGARGALLL ALLLARAGLR

         151                                                 200
Prom     SLIAAAWA.. .EEQNKLVHG GPCDKTSHPY QAALYTSGHL LCGGVLIHPL
Tryl     TFVAAALAAP FDDDDKIVGG YNCEENSVPY QVSL.NSGYH FCGGSLINEQ
Scce     LSLALETAGE EAQGDKIIDG APCARGSHPW QVALLSGNQL HCGGVLVNER
Heps     AAICQDCGRR KLPVDRIVGG RDTSLGRWPW QVSLRYDGAH LCGGSLLSGD
Tadg16   KPTIRGPCGR RVITSRIVGG EDAELGRWPW QGSLRLWDSH VCGVSLLSHR

         201                                                 250
Prom     WVLTAAHCKK ..PNLQV... .FLGKHNLRQ RESS.QEQSS VVRAVIHPDY
Tryl     WVVSAGHCYK ..SRIQV... .RLGEHNIEV LEGN.EQFIN AAKIIRHPQY
Scce     WVLTAAHCKM ..NEYTV... .HLGSDTLGD RRA...QRIK ASKSFRHPGY
Heps     WVLTAAHCFP ..ERNRVLSR WRVFAGAVAQ ASPH.GLQLG VQAVVYHGGY
Tadg16   WALTAAHCFE TYSDLSDPSG WMVQFGQLTS MPSFWSLQAY YTRYFVSNIY

         251                                                 300
Prom     ......DAAS HDQDIMLLRL ARPAKLSELI QPLPLERDCS A..NTTSCHI
Tryl     ......DRKT LNNDIMLIKL SSRAVINARV STISLPTAPP A..TGTKCLI
Scce     ......STQT HVNDLMLVKL NSQARLSSMV KKVRLPSRCE P..PGTTCTV
Heps     LPFRDPNSEE NSNDIALVHL SSPLPLTEYI QPVCLPAAGQ ALVDGKICTV
Tadg16   LSPRYLGNSP Y..DIALVKL SAPVTYTKHI QPICLQASTF EFENRTDCWV

         301                                                 350
Prom     LGWGKTAD.. G.DFPDTIQC AYIHLVSREE CEHA..YPGQ ITQNMLCAGD
Tryl     SGWGNTASSG A.DYPDELQC LDAPVLSQAK CEAS..YPGK ITSNMFCVGF
Scce     SGWGTTTSPD V.TFPSDLMC VDVKLISPQD CTKV..YKDL LENSMLCAGI
Heps     TGWGNTQYYG Q.Q.AGVLQE ARVPIISNDV CNGADFYGNQ IKPKMFCAGY
Tadg16   TGWGYIKEDE ALPSPHTLQE VQVAIINNSM CNHL.FLKYS FRKDIF..GD

         351                                                 400
Prom     EKYGKDSCQG DSGGPLVCGD HLR....... .GLVSWGNIP CGSKEKPGVY
Tryl     LEGGKDSCQG DSGGPVVCNG QLQ....... .GVVSWGD.G CAQKNKPGVY
Scce     PDSKKNACNG DSGGPLVCRG TLQ....... .GLVSWGTFP CGQPNDPGVY
Heps     PEGGIDACQG DSGGPFVCED SISRTPRWRL CGIVSWGT.G CALAQKPGVY
Tadg16   ........MG DSGGPLACN. ...KNGLWYQ IGVVSWG.VG CGRPNRPGVY

         401                                      443
Prom     TNVCRYTNWI QKTIQAK--- ---------- ---------- --- (SEQ ID NO: 3)
Tryl     TKVYNYVKWI KNTIAANS-- ---------- ---------- --- (SEQ ID NO: 4)
Scce     TQVCKFTKWI NDTMKKHR-- ---------- ---------- --- (SEQ ID NO: 5)
Heps     TKVSDFREWI FQAIKTHSEA SGMVTQL--- ---------- --- (SEQ ID NO: 6)
Tadg16   TNISHHFEWI QKLMAQSGMS QPDPSWPLLF FPLLWALPLL GPV (SEQ ID NO: 7)
```

Fig. 1

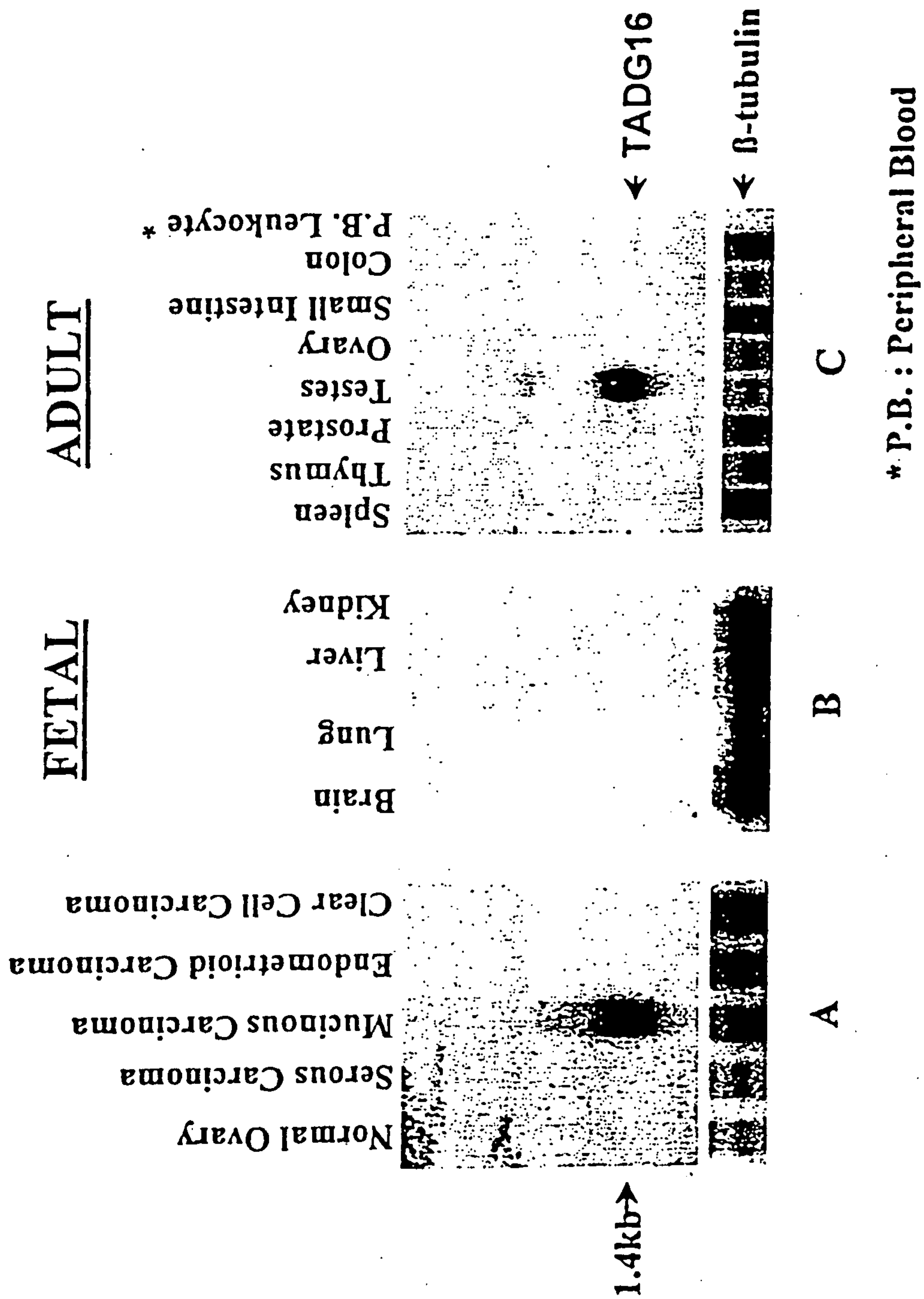
FETAL
ADULT
Normal Ovary
Serous Carcinoma
Mucinous Carcinoma
Endometrioid Carcinoma
Clear Cell Carcinoma
Brain
Lung
Liver
Kidney
Spleen
Thymus
Prostate
Testes
Ovary
Small Intestine
Colon
P.B. Leukocyte *
1.4kb
TADG16
ß-tubulin
A
B
C
* P.B. : Peripheral Blood

Fig. 2

```
1    TGGGCACTCACGGCGGCGCACTGCTTTGAAACGTATAGTGACCTTAGTGATCCCTCCGGG
     W  A  L  T  A  A  H  C  F  E  T  Y  S  D  L  S  D  P  S  G  -

60   TGGATGGTCCAGTTTGGCCAGCTGACTTCCATGCCATCCTTCTGGAGCCTGCAGGCCTAC
     W  M  V  Q  F  G  Q  L  T  S  M  P  S  F  W  S  L  Q  A  Y  -

120  TACACCCGTTACTTCGTATCGAATATCTATCTGAGCCCTCGCTACCTGGGGAATTCACCC
     Y  T  R  Y  F  V  S  N  I  Y  L  S  P  R  Y  L  G  N  S  P  -

180  TATGACATTGCCTTGGTGAAGCTGTCTGCACCTGTCACCTACACTAAACACATCCAGCCC
     Y  D  I  A  L  V  K  L  S  A  P  V  T  Y  T  K  H  I  Q  P  -

240  ATCTGTCTCCAGGCCTCCACATTTGAGTTTGAGAACCGGACAGACTGCTGGGTGACTGGC
     I  C  L  Q  A  S  T  F  E  F  E  N  R  T  D  C  W  V  T  G  -

300  TGGGGGTACATCAAAGAGGATGAGGCACTGCCATCTCCCCACACCCTCCAGGAAGTTCAG
     W  G  Y  I  K  E  D  E  A  L  P  S  P  H  T  L  Q  E  V  Q  -

360  GTCGCCATCATAAACAACTCTATGTGCAACCACCTCTTCCTCAAGTACAGTTTCCGCAAG
     V  A  I  I  N  N  S  M  C  N  H  L  F  L  K  Y  S  F  R  K  -

420  GACATCTTTGGAGACATGGTTTGTGCTGGCAATGCCCAAGGCGGGAAGGATGCCTGCTTC
     D  I  F  G  D  M  V  C  A  G  N  A  Q  G  G  K  D  A  C  F  -

480  GGTGACTCAGGTGGACCC (SEQ ID NO: 177)
     G  D  S  G  G  P   (SEQ ID NO: 178)
```

Fig. 3A

```
  1  TTTTTTTTTT TTGAAGAATG CCCTGCAAGG CATCAACTGG AATGTGTTTA
 51  TTACCAAACA AGACAGAAGA GAACCAGGGC CTGACTTGGC AGTGGCCCAG
101  GCTGCATGGG CTCAGGTAGG CTCAGACCGG CCCCAGGAGT GGGAGAGCCC
151  AGAGAAGAGG GAAAAAGAGT AGTGGCCAGG AGGGGTCTGG CTGGGACATG
201  CCACTCTGGG CCATCAGCTT CTGGATCCAC TCAAAGTGGT GGCTGATATT
251  GGTGTAGACA CCGGGCCGAT TGGGCGACCA CAGCCCACTC CCCAGCTCAC
301  GACTCCAATC TGATACCACA GTCCATTCTT GTTACAGGCC AAGGGTCCAC
351  CTGAGTCACC GAAGCAGGCA TCCTTCCCGC ACTTGGGCAT TGCCAGCACA
401  AACCATGTCT CCAAAGATGT CCTTGCGGAA ACTGTACTTG AGGAAGAGGT
451  GGTTGCACAT AGAGTTGTTT ATGATGGCGA ACTGAACTTC CTGGAGGGTG
                                             (SEQ ID NO: 179)
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Fig. 3B

1 GGGGCGCCCCGGGCCCGGCGCGAGAGGAGGCAGAGGGGGCGTCAGGCCGCGGGAGAGGAG
61 GCCATGGGCGCGCGCGGGGCGCTGCTGCTGGCGCTGCTGCTGGCTCGGGCTGGACTCAGG
M G A R G A L L L A L L L A R A G L R

121 AAGCCGGAGTCGCAGGAGGCGGCGCCGTTATCAGGACCATGCGGCCGACGGGTCATCACG
K P E S Q E A A P L S G P C G R R V I T

181 TCGCGCATCGTGGGTGGAGAGGACGCCGAACTCGGGCGTTGGCCGTGGCAGGGGAGCCTG
S R I V G G E D A E L G R W P W Q G S L

241 CGCCTGTGGGATTCCCACGTATGCGGAGTGAGCCTGCTCAGCCACCGCTGGGCACTCACG
R L W D S H V C G V S L L S H R W A L T

301 GCGGCGCACTGCTTTGAAACGTATAGTGACCTTAGTGATCCCTCCGGGTGGATGGTCCAG
A A H C F E T Y S D L S D P S G W M V Q

361 TTTGGCCAGCTGACTTCCATGCCATCCTTCTGGAGCCTGCAGGCCTACTACACCCGTTAC
F G Q L T S M P S F W S L Q A Y Y T R Y

421 TTCGTATCGAATATCTATCTGAGCCCTCGCTACCTGGGGAATTCACCCTATGACATTGCC
F V S N I Y L S P R Y L G N S P Y D I A

481 TTGGTGAAGCTGTCTGCACCTGTCACCTACACTAAACACATCCAGCCCATCTGTCTCCAG
L V K L S A P V T Y T K H I Q P I C L Q

541 GCCTCCACATTTGAGTTTGAGAACCGGACAGACTGCTGGGTGACTGGCTGGGGGTACATC
A S T F E F E N R T D C W V T G W G Y I

601 AAAGAGGATGAGGCACTGCCATCTCCCCACACCCTCCAGGAAGTTCAGGTCGCCATCATA
K E D E A L P S P H T L Q E V Q V A I I

661 AACAACTCTATGTGCAACCACCTCTTCCTCAAGTACAGTTTCCGCAAGGACATCTTTGGA
N N S M C N H L F L K Y S F R K D I F G

721 GACATGGTTTGTGCTGGCAATGCCCAAGGCGGGAAGGATGCCTGCTTCGGTGACTCAGGT
D M V C A G N A Q G G K D A C F G D S G

781 GGACCCTTGGCCTGTAACAAGAATGGACTGTGGTATCAGATTGGAGTCGTGAGCTGGGGA
G P L A C N K N G L W Y Q I G V V S W G

841 GTGGGCTGTGGTCGGCCCAATCGGCCCGGTGTCTACACCAATATCAGCCACCACTTTGAG
V G C G R P N R P G V Y T N I S H H F E

901 TGGATCCAGAAGCTGATGGCCCAGAGTGGCATGTCCCAGCCAGACCCCTCCTGGCCGCTA
W I Q K L M A Q S G M S Q P D P S W P L

961 CTCTTTTTCCCTCTTCTCTGGGCTCTCCCACTCCTGGGGCCGGTCTGAGCCTACCTGAGC
L F F P L L W A L P L L G P V * (SEQ ID NO: 2)

1021 CCATGCAGCCTGGGGCCAACTGCCAAGTCAGGCCCTGGTTCTCTTCTGTCTTGTTTGGTA
1081 ATAAACACATTCCAGTTGATGCCTTGCAGGGCATTCTTCAAAAAAAAAAAA (SEQ ID NO: 1)

Fig. 4

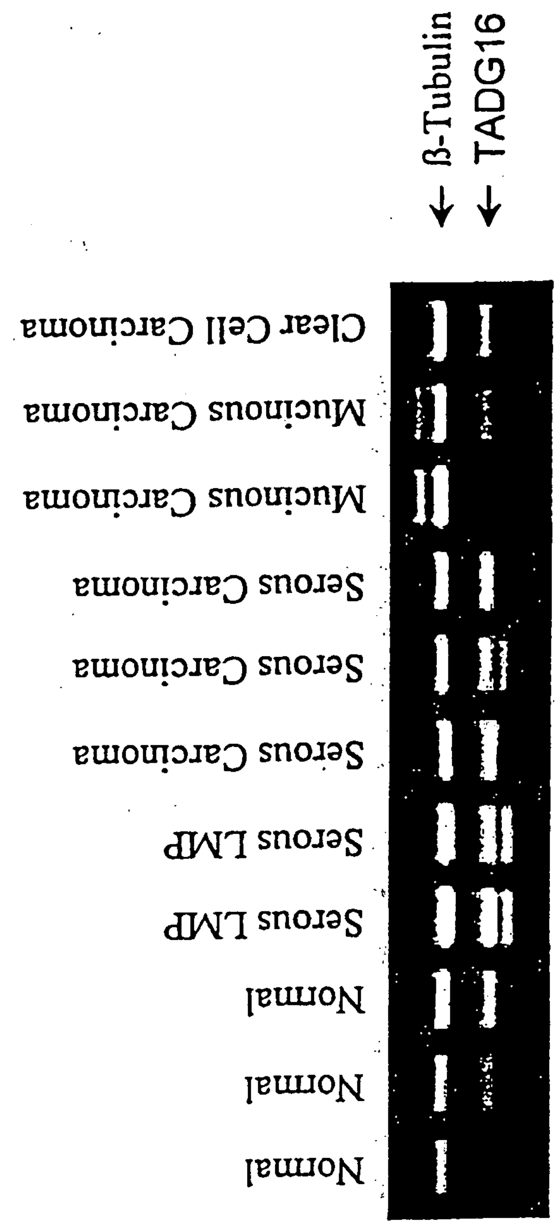
β-Tubulin
TADG16
Clear Cell Carcinoma
Mucinous Carcinoma
Mucinous Carcinoma
Serous Carcinoma
Serous Carcinoma
Serous Carcinoma
Serous LMP
Serous LMP
Normal
Normal
Normal

Fig. 5

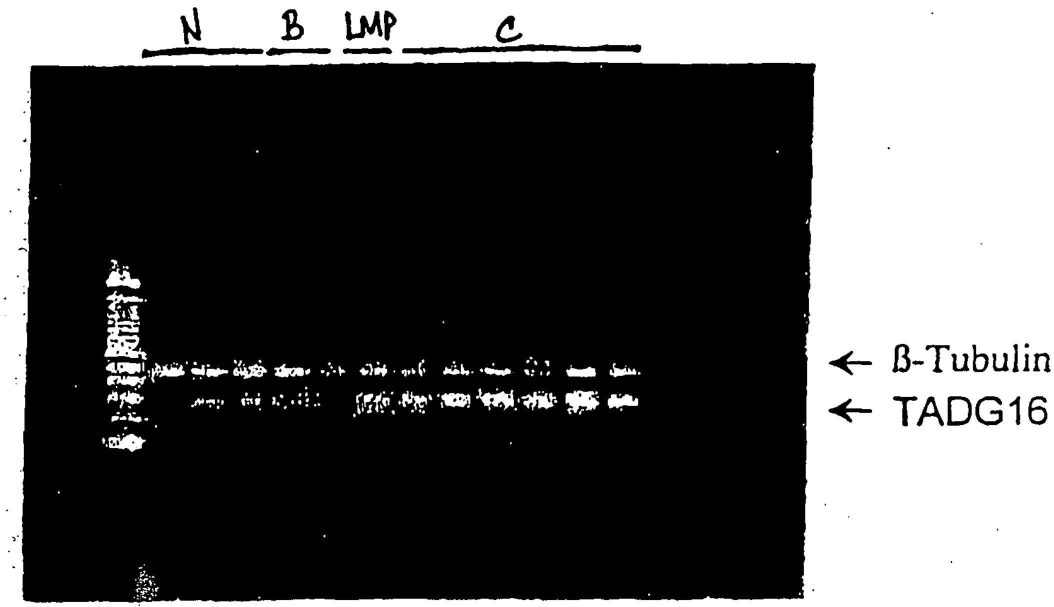
N
B
LMP
C
← ß-Tubulin
← TADG16

Fig. 6A

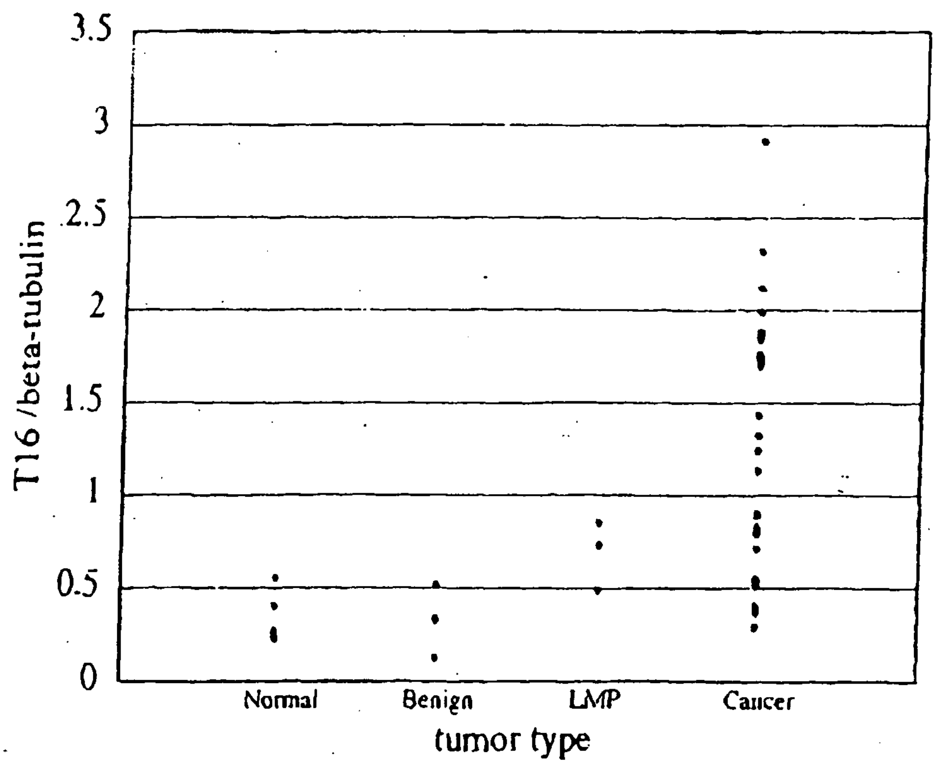
3.5
3
2.5
2
1.5
1
0.5
0
T16 /beta-tubulin
Normal
Benign
LMP
Cancer
tumor type

Fig. 6B

SEQUENCE LISTING

<110> O'Brien, Timothy J.
Underwood, Lowell
Shigemasa, Kazushi

<120> Tumor Antigen-Derived Gene 16 (TADG-16): A Novel Extracellular Serine Protease and Uses Thereof

<130> D6250PCT

<141> 2000-10-13

<150> US 09/418,527
<151> 1999-10-14

<160> 179

<210> 1
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<213> *Homo sapiens*

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tggctcgggc tggactcagg aagccggagt cgcaggaggc ggcgccgtta   150
tcaggaccat gcggccgacg ggtcatcacg tcgcgcatcg tgggtggaga   200
ggacgccgaa ctcgggcgtt ggccgtggca ggggagcctg cgcctgtggg   250
attcccacgt atgcggagtg agcctgctca gccaccgctg ggcactcacg   300
gcggcgcact gctttgaaac gtatagtgac cttagtgatc cctccgggtg   350
gatggtccag tttggccagc tgacttccat gccatccttc tggagcctgc   400
aggcctacta cacccgttac ttcgtatcga atatctatct gagccctcgc   450
tacctgggga attcacccta tgacattgcc ttggtgaagc tgtctgcacc   500
tgtcacctac actaaacaca tccagcccat ctgtctccag gcctccacat   550
ttgagtttga gaaccggaca gactgctggg tgactggctg gggtacatc    600
aaagaggatg aggcactgcc atctccccac accctccagg aagttcaggt   650
cgccatcata aacaactcta tgtgcaacca cctcttcctc aagtacagtt   700
tccgcaagga catctttgga gacatggttt gtgctggcaa tgcccaaggc   750
gggaaggatg cctgcttcgg tgactcaggt ggacccttgg cctgtaacaa   800
gaatggactg tggtatcaga ttggagtcgt gagctgggga gtgggctgtg   850
gtcggcccaa tcggcccggt gtctacacca atatcagcca ccactttgag   900
tggatccaga agctgatggc ccagagtggc atgtcccagc cagacccctc   950
ctggccgcta ctcttttcc ctcttctctg ggctctccca ctcctggggc  1000
cggtctgagc ctacctgagc ccatgcagcc tggggccaac tgccaagtca  1050
ggccctggtt ctcttctgtc ttgtttggta ataaacacat tccagttgat  1100
gccttgcagg gcattcttca aaaaaaaaa a                       1131
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<210> 2
<211> 314

<212> PRT
<213> *Homo* [illegible]*iens*

<220>
<223> TADG-16 protein sequence

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Ala Gly Leu Arg Lys Pro Glu Ser Gln Glu Ala Ala Pro Leu Ser
20 25 30
Gly Pro Cys Gly Arg Arg Val Ile Thr Ser Arg Ile Val Gly Gly
35 40 45
Glu Asp Ala Glu Leu Gly Arg Trp Pro Trp Gln Gly Ser Leu Arg
50 55 60
Leu Trp Asp Ser His Val Cys Gly Val Ser Leu Leu Ser His Arg
65 70 75
Trp Ala Leu Thr Ala Ala His Cys Phe Glu Thr Tyr Ser Asp Leu
80 85 90
Ser Asp Pro Ser Gly Trp Met Val Gln Phe Gly Gln Leu Thr Ser
95 100 105
Met Pro Ser Phe Trp Ser Leu Gln Ala Tyr Tyr Thr Arg Tyr Phe
110 115 120
Val Ser Asn Ile Tyr Leu Ser Pro Arg Tyr Leu Gly Asn Ser Pro
125 130 135
Tyr Asp Ile Ala Leu Val Lys Leu Ser Ala Pro Val Thr Tyr Thr
140 145 150
Lys His Ile Gln Pro Ile Cys Leu Gln Ala Ser Thr Phe Glu Phe
155 160 165
Glu Asn Arg Thr Asp Cys Trp Val Thr Gly Trp Gly Tyr Ile Lys
170 175 180
Glu Asp Glu Ala Leu Pro Ser Pro His Thr Leu Gln Glu Val Gln
185 190 195
Val Ala Ile Ile Asn Asn Ser Met Cys Asn His Leu Phe Leu Lys
200 205 210
Tyr Ser Phe Arg Lys Asp Ile Phe Gly Asp Met Val Cys Ala Gly
215 220 225
Asn Ala Gln Gly Gly Lys Asp Ala Cys Phe Gly Asp Ser Gly Gly
230 235 240
Pro Leu Ala Cys Asn Lys Asn Gly Leu Trp Tyr Gln Ile Gly Val
245 250 255
Val Ser Trp Gly Val Gly Cys Gly Arg Pro Asn Arg Pro Gly Val
260 265 270
Tyr Thr Asn Ile Ser His His Phe Glu Trp Ile Gln Lys Leu Met
275 280 285
Ala Gln Ser Gly Met Ser Gln Pro Asp Pro Ser Trp Pro Leu Leu
290 295 300
Phe Phe Pro Leu Leu Trp Ala Leu Pro Leu Leu Gly Pro Val
305 310

<210> 3
<211> 244
<212> PRT
<213> Unknown

<220>
<223> Sequence of Protease M

<400> 3
Met Lys Lys Leu Met Val Val Leu Ser Leu Ile Ala Ala Ala Trp
5 10 15
Ala Glu Glu Gln Asn Lys Leu Val His Gly Gly Pro Cys Asp Lys
20 25 30
Thr Ser His Pro Tyr Gln Ala Ala Leu Tyr Thr Ser Gly His Leu
35 40 45
Leu Cys Gly Gly Val Leu Ile His Pro Leu Trp Val Leu Thr Ala
50 55 60
Ala His Cys Lys Lys Pro Asn Leu Gln Val Phe Leu Gly Lys His
65 70 75
Asn Leu Arg Gln Arg Glu Ser Ser Gln Glu Gln Ser Ser Val Val
80 85 90
Arg Ala Val Ile His Pro Asp Tyr Asp Ala Ala Ser His Asp Gln
95 100 105
Asp Ile Met Leu Leu Arg Leu Ala Arg Pro Ala Lys Leu Ser Glu
110 115 120
Leu Ile Gln Pro Leu Pro Leu Glu Arg Asp Cys Ser Ala Asn Thr
125 130 135
Thr Ser Cys His Ile Leu Gly Trp Gly Lys Thr Ala Asp Gly Asp
140 145 150
Phe Pro Asp Thr Ile Gln Cys Ala Tyr Ile His Leu Val Ser Arg
155 160 165
Glu Glu Cys Glu His Ala Tyr Pro Gly Gln Ile Thr Gln Asn Met
170 175 180
Leu Cys Ala Gly Asp Glu Lys Tyr Gly Lys Asp Ser Cys Gln Gly
185 190 195
Asp Ser Gly Gly Pro Leu Val Cys Gly Asp His Leu Arg Gly Leu
200 205 210
Val Ser Trp Gly Asn Ile Pro Cys Gly Ser Lys Glu Lys Pro Gly
215 220 225
Val Tyr Thr Asn Val Cys Arg Tyr Thr Asn Trp Ile Gln Lys Thr
230 235 240
Ile Gln Ala Lys

<210> 4
<211> 247
<212> PRT
<213> Unknown

<220>
<223> Sequence of Trypsinogen

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Ala Pro Phe Asp Asp Asp Asp Lys Ile Val Gly Gly Tyr Asn Cys
20 25 30
Glu Glu Asn Ser Val Pro Tyr Gln Val Ser Leu Asn Ser Gly Tyr
35 40 45
His Phe Cys Gly Gly Ser Leu Ile Asn Glu Gln Trp Val Val Ser
50 55 60

Ala Gly His Cys Tyr Lys Ser Arg Ile Gln Val Arg Leu Gly Glu
65 70 75
His Asn Ile Glu Val Leu Glu Gly Asn Glu Gln Phe Ile Asn Ala
80 85 90
Ala Lys Ile Ile Arg His Pro Gln Tyr Asp Arg Lys Thr Leu Asn
95 100 105
Asn Asp Ile Met Leu Ile Lys Leu Ser Ser Arg Ala Val Ile Asn
110 115 120
Ala Arg Val Ser Thr Ile Ser Leu Pro Thr Ala Pro Pro Ala Thr
125 130 135
Gly Thr Lys Cys Leu Ile Ser Gly Trp Gly Asn Thr Ala Ser Ser
140 145 150
Gly Ala Asp Tyr Pro Asp Glu Leu Gln Cys Leu Asp Ala Pro Val
155 160 165
Leu Ser Gln Ala Lys Cys Glu Ala Ser Tyr Pro Gly Lys Ile Thr
170 175 180
Ser Asn Met Phe Cys Val Gly Phe Leu Glu Gly Gly Lys Asp Ser
185 190 195
Cys Gln Gly Asp Ser Gly Gly Pro Val Val Cys Asn Gly Gln Leu
200 205 210
Gln Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Lys Asn Lys
215 220 225
Pro Gly Val Tyr Thr Lys Val Tyr Asn Tyr Val Lys Trp Ile Lys
230 235 240
Asn Thr Ile Ala Ala Asn Ser
245

<210> 5
<211> 253
<212> PRT
<213> Unknown

<220>
<223> Sequence of SCCE

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Leu Ala Leu Glu Thr Ala Gly Glu Glu Ala Gln Gly Asp Lys Ile
20 25 30
Ile Asp Gly Ala Pro Cys Ala Arg Gly Ser His Pro Trp Gln Val
35 40 45
Ala Leu Leu Ser Gly Asn Gln Leu His Cys Gly Gly Val Leu Val
50 55 60
Asn Glu Arg Trp Val Leu Thr Ala Ala His Cys Lys Met Asn Glu
65 70 75
Tyr Thr Val His Leu Gly Ser Asp Thr Leu Gly Asp Arg Arg Ala
80 85 90
Gln Arg Ile Lys Ala Ser Lys Ser Phe Arg His Pro Gly Tyr Ser
95 100 105
Thr Gln Thr His Val Asn Asp Leu Met Leu Val Lys Leu Asn Ser
110 115 120
Gln Ala Arg Leu Ser Ser Met Val Lys Lys Val Arg Leu Pro Ser
125 130 135
Arg Cys Glu Pro Pro Gly Thr Thr Cys Thr Val Ser Gly Trp Gly
140 145 150

Thr Thr Thr Ser Pro Asp Val Thr Phe Pro Ser Asp Leu Met Cys
155 160 165
Val Asp Val Lys Leu Ile Ser Pro Gln Asp Cys Thr Lys Val Tyr
170 175 180
Lys Asp Leu Leu Glu Asn Ser Met Leu Cys Ala Gly Ile Pro Asp
185 190 195
Ser Lys Lys Asn Ala Cys Asn Gly Asp Ser Gly Gly Pro Leu Val
200 205 210
Cys Arg Gly Thr Leu Gln Gly Leu Val Ser Trp Gly Thr Phe Pro
215 220 225
Cys Gly Gln Pro Asn Asp Pro Gly Val Tyr Thr Gln Val Cys Lys
230 235 240
Phe Thr Lys Trp Ile Asn Asp Thr Met Lys Lys His Arg
245 250

<210> 6
<211> 421
<212> PRT
<213> Unknown

<220>
<221> PEPTIDE
<222> 1, 2, 3, 4
<223> Sequence of Hepsin, Xaa = Unknown at 1, 2, 3, 4

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Xaa Xaa Xaa Xaa Met Ala Gln Lys Glu Gly Gly Arg Thr Val Pro
5 10 15
Cys Cys Ser Arg Pro Lys Val Ala Ala Leu Thr Ala Gly Thr Leu
20 25 30
Leu Leu Leu Thr Ala Ile Gly Ala Ala Ser Trp Ala Ile Val Ala
35 40 45
Val Leu Leu Arg Ser Asp Gln Glu Pro Leu Tyr Pro Val Gln Val
50 55 60
Ser Ser Ala Asp Ala Arg Leu Met Val Phe Asp Lys Thr Glu Gly
65 70 75
Thr Trp Arg Leu Leu Cys Ser Ser Arg Ser Asn Ala Arg Val Ala
80 85 90
Gly Leu Ser Cys Glu Glu Met Gly Phe Leu Arg Ala Leu Thr His
95 100 105
Ser Glu Leu Asp Val Arg Thr Ala Gly Ala Asn Gly Thr Ser Gly
110 115 120
Phe Phe Cys Val Asp Glu Gly Arg Leu Pro His Thr Gln Arg Leu
125 130 135
Leu Glu Val Ile Ser Val Cys Asp Cys Pro Arg Gly Arg Phe Leu
140 145 150
Ala Ala Ile Cys Gln Asp Cys Gly Arg Arg Lys Leu Pro Val Asp
155 160 165
Arg Ile Val Gly Gly Arg Asp Thr Ser Leu Gly Arg Trp Pro Trp
170 175 180
Gln Val Ser Leu Arg Tyr Asp Gly Ala His Leu Cys Gly Gly Ser
185 190 195
Leu Leu Ser Gly Asp Trp Val Leu Thr Ala Ala His Cys Phe Pro
200 205 210
Glu Arg Asn Arg Val Leu Ser Arg Trp Arg Val Phe Ala Gly Ala
215 220 225

Val Ala Gln Ala Ser Pro His Gly Leu Gln Leu Gly Val Gln Ala
230 235 240
Val Val Tyr His Gly Gly Tyr Leu Pro Phe Arg Asp Pro Asn Ser
245 250 255
Glu Glu Asn Ser Asn Asp Ile Ala Leu Val His Leu Ser Ser Pro
260 265 270
Leu Pro Leu Thr Glu Tyr Ile Gln Pro Val Cys Leu Pro Ala Ala
275 280 285
Gly Gln Ala Leu Val Asp Gly Lys Ile Cys Thr Val Thr Gly Trp
290 295 300
Gly Asn Thr Gln Tyr Tyr Gly Gln Gln Ala Gly Val Leu Gln Glu
305 310 315
Ala Arg Val Pro Ile Ile Ser Asn Asp Val Cys Asn Gly Ala Asp
320 325 330
Phe Tyr Gly Asn Gln Ile Lys Pro Lys Met Phe Cys Ala Gly Tyr
335 340 345
Pro Glu Gly Gly Ile Asp Ala Cys Gln Gly Asp Ser Gly Gly Pro
350 355 360
Phe Val Cys Glu Asp Ser Ile Ser Arg Thr Pro Arg Trp Arg Leu
365 370 375
Cys Gly Ile Val Ser Trp Gly Thr Gly Cys Ala Leu Ala Gln Lys
380 385 390
Pro Gly Val Tyr Thr Lys Val Ser Asp Phe Arg Glu Trp Ile Phe
395 400 405
Gln Ala Ile Lys Thr His Ser Glu Ala Ser Gly Met Val Thr Gln
410 415 420
Leu

<210> 7
<211> 294
<212> PRT
<213> *Homo sapiens*

<220>
<223> TADG-16 protein sequence

<400> 7

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Ala Gly Leu Arg Lys Pro Thr Ile Arg Gly Pro Cys Gly Arg Arg
20 25 30
Val Ile Thr Ser Arg Ile Val Gly Gly Glu Asp Ala Glu Leu Gly
35 40 45
Arg Trp Pro Trp Gln Gly Ser Leu Arg Leu Trp Asp Ser His Val
50 55 60
Cys Gly Val Ser Leu Leu Ser His Arg Trp Ala Leu Thr Ala Ala
65 70 75
His Cys Phe Glu Thr Tyr Ser Asp Leu Ser Asp Pro Ser Gly Trp
80 85 90
Met Val Gln Phe Gly Gln Leu Thr Ser Met Pro Ser Phe Trp Ser
95 100 105
Leu Gln Ala Tyr Tyr Thr Arg Tyr Phe Val Ser Asn Ile Tyr Leu
110 115 120
Ser Pro Arg Tyr Leu Gly Asn Ser Pro Tyr Asp Ile Ala Leu Val
125 130 135

Lys Leu Ser [illegible] Pro Val Thr Tyr Thr Lys H[illegible] Ile Gln Pro Ile
140 145 150
Cys Leu Gln Ala Ser Thr Phe Glu Phe Glu Asn Arg Thr Asp Cys
155 160 165
Trp Val Thr Gly Trp Gly Tyr Ile Lys Glu Asp Glu Ala Leu Pro
170 175 180
Ser Pro His Thr Leu Gln Glu Val Gln Val Ala Ile Ile Asn Asn
185 190 195
Ser Met Cys Asn His Leu Phe Leu Lys Tyr Ser Phe Arg Lys Asp
200 205 210
Ile Phe Gly Asp Met Gly Asp Ser Gly Gly Pro Leu Ala Cys Asn
215 220 225
Lys Asn Gly Leu Trp Tyr Gln Ile Gly Val Val Ser Trp Gly Val
230 235 240
Gly Cys Gly Arg Pro Asn Arg Pro Gly Val Tyr Thr Asn Ile Ser
245 250 255
His His Phe Glu Trp Ile Gln Lys Leu Met Ala Gln Ser Gly Met
260 265 270
Ser Gln Pro Asp Pro Ser Trp Pro Leu Leu Phe Phe Pro Leu Leu
275 280 285
Trp Ala Leu Pro Leu Leu Gly Pro Val
290

<210> 8
<211> 23
<212> DNA
<213> Artificial sequence

<220>
<221> primer_bind
<222> 6, 9, 12, 15, 18
<223> Degenerate oligonucleotide sense primer to amplify serine proteases, n = inosine at 6, 9, 12, 15, 18

<400> 8
tgggtngtna cngcngcnca ytg 23

<210> 9
<211> 20
<212> DNA
<213> Artificial sequence

<220>
<221> primer_bind
<222> 3, 6, 9, 12, 18
<223> Degenerate oligonucleotide antisense primer to amplify serine proteases, n = inosine at 3, 6, 9, 12, 18

<400> 9
arnggnccnc cnswrtcncc 20

<210> 10
<211> 20
<212> DNA
<213> Artificial sequence

<220>
<223> Oligonucleotide sense primer specific for TADG-16

<400> 10
gtcaggccgc gggagaggag 20

<210> 11
<211> 20
<212> DNA
<213> Artificial sequence

<220>
<223> Oligonucleotide antisense primer specific for TADG-16

<400> 11
actctgggcc atcagcttct 20

<210> 12
<211> 28
<212> DNA
<213> Artificial sequence

<220>
<223> Oligonucleotide antisense primer specific for TADG-16

<400> 12
cggagggatc actaaggtca ctatacgt 28

<210> 13
<211> 28
<212> DNA
<213> Artificial sequence

<220>
<223> Oligonucleotide antisense primer specific for TADG-16

<400> 13
tatacgtttc aaagcagtgc gccgccgt 28

<210> 14
<211> 20
<212> DNA
<213> Artificial sequence

<220>
<223> Oligonucleotide sense primer specific for TADG-16

<400> 14
ggtcgccatc ataaacaact 20

<210> 15
<211> 20
<212> DNA
<213> Artificial sequence

<220>

<223> Oligonucleotide antisense primer specific for TADG-16

<400> 15
actctgggcc atcagcttct 20

<210> 16
<211> 1131
<212> RNA
<213> Artificial sequence

<220>
<223> Antisense transcript of TADG-16

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uuaccaaaca agacagaaga gaaccagggc cugacuuggc aguuggcccc 100
aggcugcaug ggcucaggua ggcucagacc ggccccagga gugggagagc 150
ccagagaaga gggaaaaaga guagcggcca ggaggggucu ggcugggaca 200
ugccacucug ggccaucagc uucuggaucc acucaaagug guggcugaua 250
uugguguaga caccgggccg auugggccga ccacagccca cuccccagcu 300
cacgacucca aucugauacc acaguccauu cuuguuacag gccaaggguc 350
caccugaguc accgaagcag gcauccuucc cgccuugggc auugccagca 400
caaaccaugu cuccaaagau guccuugcgg aaacuguacu ugaggaagag 450
gugguugcac auagaguugu uuaugauggc gaccugaacu uccuggaggg 500
uguggggaga uggcagugcc ucauccucuu ugauguaccc ccagccaguc 550
acccagcagu cuguccgguu cucaaacuca aauguggagg ccuggagaca 600
gaugggcugg auguguuuag uguaggugac aggugcagac agcuucacca 650
aggcaauguc auagggugaa uuccccaggu agcgagggcu cagauagaua 700
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ggucacuaua cguuucaaag cagugcgccg ccgugagugc ccagcggugg 850
cugagcaggc ucacuccgca uacgugggaa ucccacaggc gcaggcuccc 900
cugccacggc caacgcccga guucggcguc cucuccaccc acgaugcgcg 950
acgugaugac ccgucggccg cauggguccug auaacggcgc cgccuccugc 1000
gacuccggcu uccugagucc agcccgagcc agcagcagcg ccagcagcag 1050
cgccccgcgc gcgcccaugg ccuccucucc cgcggccuga cgcccccucu 1100
gccuccucuc gcgccgggcc cggggcgccc c 1131

<210> 17
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 70-78 of the TADG-16 protein

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<210> 18
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 299-307 of the TADG-16 protein

<400> 18
Leu Leu Phe Phe Pro Leu Leu Trp Ala
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<210> 19
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 142-150 of the TADG-16 protein

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<210> 20
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 96-104 of the TADG-16 protein

<400> 20
Trp Met Val Gln Phe Gly Gln Leu Thr
5

<210> 21
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 10-18 of the TADG-16 protein

<400> 21
Ala Leu Leu Leu Ala Arg Ala Gly Leu
5

<210> 22
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 252-260 of the TADG-16 protein

<400> 22
Gln Ile Gly Val Val Ser Trp Gly Val
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<210> 23
<211> 9
<212> PRT
<213> *Homo sapiens*

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<210> 24
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<213> *Homo sapiens*

<220>
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<210> 25
<211> 9
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<213> *Homo sapiens*

<220>
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<210> 26
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 130-138 of the TADG-16 protein

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5

<210> 27
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 190-198 of the TADG-16 protein

<400> 27
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5

<210> 28
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 6-14 of the TADG-16 protein

<400> 28
Ala Leu Leu Leu Ala Leu Leu Leu Ala
5

<210> 29
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 165-173 of the TADG-16 protein

<400> 29
Phe Glu Asn Arg Thr Asp Cys Trp Val
5

<210> 30
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 71-79 of the TADG-16 protein

<400> 30
Leu Leu Ser His Arg Trp Ala Leu Thr
5

<210> 31
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 8-16 of the TADG-16 protein

<400> 31
Leu Leu Ala Leu Leu Leu Ala Arg Ala
5

<210> 32
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 297-305 of the TADG-16 protein

<400> 32
Trp Pro Leu Leu Phe Phe Pro Leu Leu
5

<210> 33
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 113-121 of the TADG-16 protein

<400> 33
Gln Ala Tyr Tyr Thr Arg Tyr Phe Val
5

<210> 34
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 123-131 of the TADG-16 protein

<400> 34
Asn Ile Tyr Leu Ser Pro Arg Tyr Leu
5

<210> 35
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 104-112 of the TADG-16 protein

<400> 35
Thr Ser Met Pro Ser Phe Trp Ser Leu
5

<210> 36
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 273-281 of the TADG-16 protein

<400> 36
Asn Ile Ser His His Phe Glu Trp Ile
5

<210> 37
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 70-78 of the TADG-16 protein

<400> 37
Ser Leu Leu Ser His Arg Trp Ala Leu
5

<210> 38
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 42-50 of the TADG-16 protein

<400> 38
Ile Val Gly Gly Glu Asp Ala Glu Leu
5

<210> 39
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 10-18 of the TADG-16 protein

<400> 39
Ala Leu Leu Leu Ala Arg Ala Gly Leu
5

<210> 40
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 291-299 of the TADG-16 protein

<400> 40
Ser Gln Pro Asp Pro Ser Trp Pro Leu
5

<210> 41
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 297-305 of the TADG-16 protein

<400> 41
Trp Pro Leu L[illegible] Phe Phe Pro Leu Leu
5

<210> 42
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 248-256 of the TADG-16 protein

<400> 42
Gly Leu Trp Tyr Gln Ile Gly Val Val
5

<210> 43
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 82-90 of the TADG-16 protein

<400> 43
His Cys Phe Glu Thr Tyr Ser Asp Leu
5

<210> 44
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 142-150 of the TADG-16 protein

<400> 44
Lys Leu Ser Ala Pro Val Thr Tyr Thr
5

<210> 45
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 96-104 of the TADG-16 protein

<400> 45
Trp Met Val Gln Phe Gly Gln Leu Thr
5

<210> 46
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 299-307 of the TADG-16 protein

<400> 46
Leu Leu Phe Phe Pro Leu Leu Trp Ala
5

<210> 47
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 303-311 of the TADG-16 protein

<400> 47
Pro Leu Leu Trp Ala Leu Pro Leu Leu
5

<210> 48
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 123-131 of the TADG-16 protein

<400> 48
Asn Ile Tyr Leu Ser Pro Arg Tyr Leu
5

<210> 49
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 98-106 of the TADG-16 protein

<400> 49
Val Gln Phe Gly Gln Leu Thr Ser Met
5

<210> 50
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 306-314 of the TADG-16 protein

<400> 50
Trp Ala Leu Pro Leu Leu Gly Pro Val
5

<210> 51
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 71-79 of the TADG-16 protein

<400> 51
Leu Leu Ser His Arg Trp Ala Leu Thr
5

<210> 52
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 53-61 of the TADG-16 protein

<400> 52
Trp Pro Trp Gln Gly Ser Leu Arg Leu
5

<210> 53
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 302-310 of the TADG-16 protein

<400> 53
Phe Pro Leu Leu Trp Ala Leu Pro Leu
5

<210> 54
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 130-138 of the TADG-16 protein

<400> 54
Tyr Leu Gly Asn Ser Pro Tyr Asp Ile
5

<210> 55
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 6-14 of the TADG-16 protein

<400> 55
Ala Leu Leu [illegible] Ala Leu Leu Leu Ala
5

<210> 56
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 190-198 of the TADG-16 protein

<400> 56
Thr Leu Gln Glu Val Gln Val Ala Ile
5

<210> 57
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 44-52 of the TADG-16 protein

<400> 57
Gly Gly Glu Asp Ala Glu Leu Gly Arg
5

<210> 58
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 90-98 of the TADG-16 protein

<400> 58
Leu Ser Asp Pro Ser Gly Trp Met Val
5

<210> 59
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 143-151 of the TADG-16 protein

<400> 59
Leu Ser Ala Pro Val Thr Tyr Thr Lys
5

<210> 60
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 292-300 of the TADG-16 protein

<400> 60
Gln Pro Asp Pro Ser Trp Pro Leu Leu
5

<210> 61
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 203-211 of the TADG-16 protein

<400> 61
Met Cys Asn His Leu Phe Leu Lys Tyr
5

<210> 62
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 87-95 of the TADG-16 protein

<400> 62
Tyr Ser Asp Leu Ser Asp Pro Ser Gly
5

<210> 63
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 168-176 of the TADG-16 protein

<400> 63
Arg Thr Asp Cys Trp Val Thr Gly Trp
5

<210> 64
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 47-55 of the TADG-16 protein

<400> 64
Asp Ala Glu Leu Gly Arg Trp Pro Trp
5

<210> 65
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 23-31 of the TADG-16 protein

<400> 65
Ser Gln Glu Ala Ala Pro Leu Ser Gly
5

<210> 66
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 7-15 of the TADG-16 protein

<400> 66
Leu Leu Leu Ala Leu Leu Leu Ala Arg
5

<210> 67
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 157-165 of the TADG-16 protein

<400> 67
Cys Leu Gln Ala Ser Thr Phe Glu Phe
5

<210> 68
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 202-210 of the TADG-16 protein

<400> 68
Ser Met Cys Asn His Leu Phe Leu Lys
5

<210> 69
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 111-119 of the TADG-16 protein

<400> 69
Ser Leu Gln Ala Tyr Tyr Thr Arg Tyr
5

<210> 70
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 125-133 of the TADG-16 protein

<400> 70
Tyr Leu Ser Pro Arg Tyr Leu Gly Asn
5

<210> 71
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 152-160 of the TADG-16 protein

<400> 71
His Ile Gln Pro Ile Cys Leu Gln Ala
5

<210> 72
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 79-87 of the TADG-16 protein

<400> 72
Thr Ala Ala His Cys Phe Glu Thr Tyr
5

<210> 73
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 238-246 of the TADG-16 protein

<400> 73
Ser Gly Gly Pro Leu Ala Cys Asn Lys
5

<210> 74
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 172-180 of the TADG-16 protein

<400> 74
Trp Val Thr Gly Trp Gly Tyr Ile Lys
5

<210> 75
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 110-118 of the TADG-16 protein

<400> 75
Trp Ser Leu Gln Ala Tyr Tyr Thr Arg
5

<210> 76
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 191-199 of the TADG-16 protein

<400> 76
Leu Gln Glu Val Gln Val Ala Ile Ile
5

<210> 77
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 118-126 of the TADG-16 protein

<400> 77
Arg Tyr Phe Val Ser Asn Ile Tyr Leu
5

<210> 78
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 177-185 of the TADG-16 protein

<400> 78
Gly Tyr Ile Lys Glu Asp Glu Ala Leu
5

<210> 79
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 210-218 of the TADG-16 protein

<400> 79
Lys Tyr Ser Phe Arg Lys Asp Ile Phe
5

<210> 80
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 270-278 of the TADG-16 protein

<400> 80
Val Tyr Thr Asn Ile Ser His His Phe
5

<210> 81
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 148-156 of the TADG-16 protein

<400> 81
Thr Tyr Thr Lys His Ile Gln Pro Ile
5

<210> 82
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 300-308 of the TADG-16 protein

<400> 82
Leu Phe Phe Pro Leu Leu Trp Ala Leu
5

<210> 83
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 234-242 of the TADG-16 protein

<400> 83
Cys Phe Gly [illegible] Ser Gly Gly Pro Leu
5

<210> 84
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 135-143 of the TADG-16 protein

<400> 84
Pro Tyr Asp Ile Ala Leu Val Lys Leu
5

<210> 85
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 4-12 of the TADG-16 protein

<400> 85
Arg Gly Ala Leu Leu Leu Ala Leu Leu
5

<210> 86
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 104-112 of the TADG-16 protein

<400> 86
Thr Ser Met Pro Ser Phe Trp Ser Leu
5

<210> 87
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 296-304 of the TADG-16 protein

<400> 87
Ser Trp Pro Leu Leu Phe Phe Pro Leu
5

<210> 88
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 250-258 of the TADG-16 protein

<400> 88
Trp Tyr Gln Ile Gly Val Val Ser Trp
5

<210> 89
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 5-13 of the TADG-16 protein

<400> 89
Gly Ala Leu Leu Leu Ala Leu Leu Leu
5

<210> 90
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 95-103 of the TADG-16 protein

<400> 90
Gly Trp Met Val Gln Phe Gly Gln Leu
5

<210> 91
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 199-207 of the TADG-16 protein

<400> 91
Ile Asn Asn Ser Met Cys Asn His Leu
5

<210> 92
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 297-305 of the TADG-16 protein

<400> 92
Trp Pro Leu Leu Phe Phe Pro Leu Leu
5

<210> 93
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 291-299 of the TADG-16 protein

<400> 93
Ser Gln Pro Asp Pro Ser Trp Pro Leu
5

<210> 94
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 183-191 of the TADG-16 protein

<400> 94
Glu Ala Leu Pro Ser Pro His Thr Leu
5

<210> 95
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 86-94 of the TADG-16 protein

<400> 95
Thr Tyr Ser Asp Leu Ser Asp Pro Ser
5

<210> 96
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 10-18 of the TADG-16 protein

<400> 96
Ala Leu Leu Leu Ala Arg Ala Gly Leu
5

<210> 97
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 297-305 of the TADG-16 protein

<400> 97
Trp Pro Leu Leu Phe Phe Pro Leu Leu
5

<210> 98
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 302-310 of the TADG-16 protein

<400> 98
Phe Pro Leu Leu Trp Ala Leu Pro Leu
5

<210> 99
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 53-61 of the TADG-16 protein

<400> 99
Trp Pro Trp Gln Gly Ser Leu Arg Leu
5

<210> 100
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 292-300 of the TADG-16 protein

<400> 100
Gln Pro Asp Pro Ser Trp Pro Leu Leu
5

<210> 101
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 145-153 of the TADG-16 protein

<400> 101
Ala Pro Val Thr Tyr Thr Lys His Ile
5

<210> 102
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 42-50 of the TADG-16 protein

<400> 102
Ile Val Gly Gly Glu Asp Ala Glu Leu
5

<210> 103
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 10-18 of the TADG-16 protein

<400> 103
Ala Leu Leu Leu Ala Arg Ala Gly Leu
5

<210> 104
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 104-112 of the TADG-16 protein

<400> 104
Thr Ser Met Pro Ser Phe Trp Ser Leu
5

<210> 105
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 183-191 of the TADG-16 protein

<400> 105
Glu Ala Leu Pro Ser Pro His Thr Leu
5

<210> 106
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 201-209 of the TADG-16 protein

<400> 106
Asn Ser Met Cys Asn His Leu Phe Leu
5

<210> 107
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 5-13 of the TADG-16 protein

<400> 107
Gly Ala Leu Leu Leu Ala Leu Leu Leu
5

<210> 108
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 291-299 of the TADG-16 protein

<400> 108
Ser Gln Pro Asp Pro Ser Trp Pro Leu
5

<210> 109
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 70-78 of the TADG-16 protein

<400> 109
Ser Leu Leu Ser His Arg Trp Ala Leu
5

<210> 110
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 195-203 of the TADG-16 protein

<400> 110
Gln Val Ala Ile Ile Asn Asn Ser Met
5

<210> 111
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 116-124 of the TADG-16 protein

<400> 111
Tyr Thr Arg [illegible] Phe Val Ser Asn Ile
5

<210> 112
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 199-207 of the TADG-16 protein

<400> 112
Ile Asn Asn Ser Met Cys Asn His Leu
5

<210> 113
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 82-90 of the TADG-16 protein

<400> 113
His Cys Phe Glu Thr Tyr Ser Asp Leu
5

<210> 114
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 132-140 of the TADG-16 protein

<400> 114
Gly Asn Ser Pro Tyr Asp Ile Ala Leu
5

<210> 115
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 1-9 of the TADG-16 protein

<400> 115
Met Gly Ala Arg Gly Ala Leu Leu Leu
5

<210> 116
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 63-71 of the TADG-16 protein

<400> 116
Asp Ser His Val Cys Gly Val Ser Leu
5

<210> 117
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 183-191 of the TADG-16 protein

<400> 117
Glu Ala Leu Pro Ser Pro His Thr Leu
5

<210> 118
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 58-66 of the TADG-16 protein

<400> 118
Ser Leu Arg Leu Trp Asp Ser His Val
5

<210> 119
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 82-90 of the TADG-16 protein

<400> 119
His Cys Phe Glu Thr Tyr Ser Asp Leu
5

<210> 120
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 116-124 of the TADG-16 protein

<400> 120
Tyr Thr Arg Tyr Phe Val Ser Asn Ile
5

<210> 121
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 2-10 of the TADG-16 protein

<400> 121
Gly Ala Arg Gly Ala Leu Leu Leu Ala
5

<210> 122
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 302-310 of the TADG-16 protein

<400> 122
Phe Pro Leu Leu Trp Ala Leu Pro Leu
5

<210> 123
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 53-61 of the TADG-16 protein

<400> 123
Trp Pro Trp Gln Gly Ser Leu Arg Leu
5

<210> 124
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 31-39 of the TADG-16 protein

<400> 124
Gly Pro Cys Gly Arg Arg Val Ile Thr
5

<210> 125
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 297-305 of the TADG-16 protein

<400> 125
Trp Pro Leu [illegible] Phe Phe Pro Leu Leu
5

<210> 126
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 5-13 of the TADG-16 protein

<400> 126
Gly Ala Leu Leu Leu Ala Leu Leu Leu
5

<210> 127
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 71-79 of the TADG-16 protein

<400> 127
Leu Leu Ser His Arg Trp Ala Leu Thr
5

<210> 128
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 242-250 of the TADG-16 protein

<400> 128
Leu Ala Cys Asn Lys Asn Gly Leu Trp
5

<210> 129
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 10-18 of the TADG-16 protein

<400> 129
Ala Leu Leu Leu Ala Arg Ala Gly Leu
5

<210> 130
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 70-78 of the TADG-16 protein

<400> 130
Ser Leu Leu Ser His Arg Trp Ala Leu
5

<210> 131
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 63-71 of the TADG-16 protein

<400> 131
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<213> *Homo sapiens*

<220>
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<210> 136
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
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<210> 137
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<212> PRT
<213> *Homo sapiens*

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<210> 138
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<212> PRT
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<210> 139
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
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<210> 141
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<212> PRT
<213> *Homo sapiens*

<220>
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<210> 142
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<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 266-274 of the TADG-16 protein

<400> 142
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<210> 143
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<212> PRT
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<220>
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<210> 144
<211> 9
<212> PRT
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<220>
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<210> 145
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<220>
<223> Residues 213-221 of the TADG-16 protein

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<210> 146
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<212> PRT
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<210> 147
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<212> PRT
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<210> 148
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<210> 149
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<210> 150
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<212> PRT
<213> *Homo sapiens*

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<223> Residues 40-48 of the TADG-16 protein

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<210> 151
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<212> PRT
<213> *Homo sapiens*

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<210> 152
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<220>
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<210> 153
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<213> *Homo sapiens*

<220>
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Ser Gln Pro Asp Pro Ser Trp Pro Leu
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<210> 156
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<210> 157
<211> 9
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<210> 158
<211> 9

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<213> *Homo sapiens*

<220>
<223> Residues 182-190 of the TADG-16 protein

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Asp Glu Ala Leu Pro Ser Pro His Thr
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<210> 159
<211> 9
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<220>
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<210> 165
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<210> 166
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<220>
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<210> 167
<211> 9
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<213> *Homo sapiens*

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<210> 168
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<210> 170
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<212> PRT
<213> *Homo sapiens*

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<210> 171
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<213> *Homo sapiens*

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<210> 175
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Thr Asn Ile Ser His His Phe Glu Trp
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<210> 176
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 227-235 of the TADG-16 protein

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<210> 178
<211> 166
<212> PRT
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<220>
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35 40 45
Val Ser Asn Ile Tyr Leu Ser Pro Arg Tyr Leu Gly Asn Ser Pro
50 55 60
Tyr Asp Ile Ala Leu Val Lys Ser Leu Ala Pro Val Thr Tyr Thr
65 70 75
Lys His Ile Gln Pro Ile Cys Leu Gln Ala Ser Thr Phe Glu Phe
80 85 90
Glu Asn Arg Thr Asp Cys Trp Val Thr Gly Trp Gly Tyr Ile Lys
95 100 105
Glu Asp Glu Ala Leu Pro Ser Pro His Thr Leu Gln Glu Val Gln
110 115 120
Val Ala Ile Ile Asn Asn Ser Met Cys Asn His Leu Phe Leu Lys
125 130 135
Tyr Ser Phe Arg Lys Asp Ile Phe Gly Asp Met Val Cys Ala Gly
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<213> Unkno
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/28558

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12N 15/00, 5/00; C12P 21/06; C07H 21/02
US CL : 435/ 320.1, 325, 69.1; 536/ 23.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/ 320.1, 325, 69.1; 536/ 23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	HOOPER et al., GENBANK (Accession No. AF058300), National Library of Medicine, Bethesda MD., July 1, 1999 (01.04.1999)	1-4, 9-10 --- 6-7,11
X --- Y	INOUE, M. et al., Cloning and tissue distribution of a novel serine protease esp-1 from human eosinophils. Biochem. Biophys. Res. Commun. November 1998, Vol. 252, No. 2, pages 307-312.	1-4, 6-10 --- 11
X --- Y	INOUE, M. et al., GENBANK (Accession No. AB031329), National Library of Medicine, Bethesda MD., November 1998, (DNA encoding protein)	1-4, 6-10 --- 11
X --- Y	ONO PHARM CO LTD., GENBANK (Accession No. X15336), National Library of Medicine, Bethesda MD., May 4, 1999 (04.05.1999)	1-3 --- 4-7, 9-11
X	WO 98/36054 a1 (AMRAD OPERATIONS PTY. LTD.) 20 August 1998 (20.08.1998), see Fig.6, see also pages 14, 33, 38, and 40)	1, 3-7, 9-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 January 2001 (08.01.2001)	25 JAN 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Gary Nickol Telephone No. 703-308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/28558

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-11

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-11, drawn to DNA encoding a TADG-16 protein.

Group 2, claim(s) 12-13, drawn to isolated and purified TADG-16 protein.

Group 3, claim(s) 14, drawn to an antibody.

Group 4, claim(s) 15-20, drawn to a method for detecting TADG-16 mRNA.

Group 5, claim(s) 21-26, drawn to a method for detecting TADG-16 protein.

Group 6, claim(s) 27-28, drawn to a method of inhibiting endogenous expression of TADG-16 in a cell.

Group 7, claim(s) 29-30, drawn to a method of treating a neoplastic state in an individual.

Group 8, claim(s) 31-37, drawn to a method of vaccinating an individual with a TADG-16 fragment or an immunogenic composition consisting of SEQ ID NOs: 17-19, 77-80, 97-99.

Group 9, claim(s) 31-37, drawn to a method of vaccinating an individual with a TADG-16 fragment or an immunogenic composition consisting of SEQ ID NOs: 137-140.

Group 10, claim(s) 31-37, drawn to a method of vaccinating an individual with a TADG-16 fragment or an immunogenic composition consisting of SEQ ID NO: 141.

Group 11, claim(s) 38-41, drawn to a method of diagnosing cancer in an individual.

Group 12, claim(s) 42, drawn to a method of screening for compounds that inhibit TADG-16 .

Group 13, claim(s) 43-46, drawn to a method of targeted therapy to an individual.

The inventions listed as Groups 1-11 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Antalis et al. (WO/9836054, August 1998) teach an isolated DNA encoding a tumor antigen which 100% sequence similarity to SEQ ID NO:2 and or a TADG -16 protein (see Fig 6 and attached sequence comparison).